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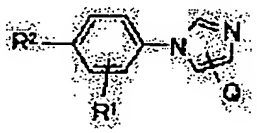
(54) IMIDAZOLE DERIVATIVE

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a medicine which inhibits 20-HETE-producing enzyme associated with microvascular constriction, dilation action, cell growth causing action, etc., in main organs such as the kidney, the cerebral blood vessel, etc.
SOLUTION: The 20-HETE-producing enzyme comprises an imidazole derivative represented by the formula {Q is a hydrogen atom or a 1-4C alkyl group; R1 is a hydrogen atom, a 1-6C alkyl group or a halogen atom; R2 is a 1-14C alkyl group, a 2-14C alkanoyl group, a morpholino group or a group represented by the formula: R3-O [R3 is a 1-14C alkyl group, a 2-14C alkenyl group, a 3-14C alkynyl group, a 3-10C cycloalkyl group, a 1-phenyl-2-propynyl group or a group represented by formula R4-A]} or its pharmaceutically permissible salt as an active ingredient.



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* NOTICES *

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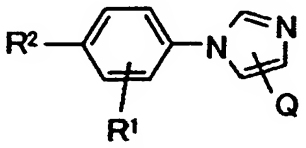
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

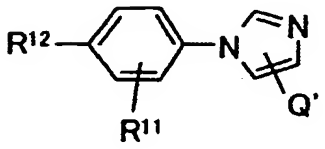
[Detailed Description of the Invention]
[0001]
[Field of the Invention]
This invention relates to the imidazole derivative which prevents the production enzyme of 20-hydroxyeicosatetraenoic acid (20-HETE) by which a biosynthesis is carried out from an arachidonic acid.
[0002]
[Description of the Prior Art]
The leukotrienes produced as a physiological active substance produced from an arachidonic acid by the prostagladins and RIPOKISHIGENAGE which are produced by cyclooxygenase are known widely. However, to carry out the work with 20-HETE variegated in the living body produced from an arachidonic acid with the enzyme belonging to cytochrome p450 group is being shown clearly in recent years. It is shown clearly until now that setting 20-HETE to main organs, such as the kidney and a cerebral blood vessel, and making a microvessel contracting or extending and cell proliferation are caused. While performing the important physiological function in the living body, various kidney disease, the cerebrovascular disease, participating in symptoms, such as cardiovascular disease, deeply is suggested (J.Vascular Research -- the 79th page the 32nd volume in 1995) Am.J.Physiol., R of 277th volume 607 pages, 1999, Physiol.Rev., the 82nd volume, the 131st term, 2002.
[0003]
Moreover, many compounds of this invention and compounds which have similar structure are reported. For example, it is reported that the derivative whose R2 is a permutation C1 - C4 alkyl group has nit rucksack oxide synthetic enzyme inhibition activity in a formula (1) (International Patent Publication WO No. 9715555 specification). It is reported that the derivative whose R2 is a permutation alkanoyl radical has cranial nerve cell death depressor effect in a formula (1) (International Patent Publication WO No. 9418172 specification). Moreover, it is reported that the derivative whose R2 is a permutation phenylalkoxy radical is effective in preventing hyperlipemia or arteriosclerosis in a formula (1) (International Patent Publication WO No. 9529163 specification). And it is reported that the derivative whose R2 is a permutation alkoxy group is effective as anti-arrhythmia, preventing hypertension, or a high ischemia therapy agent in a formula (1) (the European Patent public presentation EP No. 0306440 specification, U.S. Pat. No. 5202346 number specification). However, having 20-HETE production enzyme ****** also in any is not reported.
[0004]
On the other hand, it is reported that an imidazolyl benzophenone derivative shows 20-HETE production enzyme ******, and ** cannot necessarily satisfy the (International Patent Publication WO No. 0168610 specification), activity, or physical properties.
[0005]
[Problem(s) to be Solved by the Invention]
This invention aims at offering the drugs which check production of 20-HETE which participates in the microvessel contraction in main organs, such as the kidney and a cerebral blood vessel, an

escape, or cell proliferation inducement.
[0006]
[Means for Solving the Problem]
this invention persons completed a header and this invention for the aromatic compound which has a certain unique substructure, and the 1-(4-permutation phenyl)-1H-imidazole derivative which has various substituents especially having the inhibitory action of the production enzyme of 20-HETE unexpectedly and alternatively, as a result of doing retrieval research wholeheartedly in order to solve said technical problem.
[0007]
That is, this invention is the following type (1).
[0008]
[Formula 3]



(1)

[0009]
Q is a hydrogen atom, or C1 - C4 alkyl group among [type. R1 They are a hydrogen atom, C1 - C6 alkyl group, and a halogen atom. R2 R3 among C1 - C14 alkyl group, C2 - C14 alkanoyl radical, a morpholino radical, or a formula R3-O-[type C1 - C14 alkyl group, C2 - C14 alkenyl radical, C3 - C14 alkynyl group, C3 - C10 cycloalkyl radical, 1-phenyl-2-propynyl group, or formula R4-A - (among a formula) R4 C3 - C10 cycloalkyl radical, C1 - C10 alkoxy group, C2 - C10 alkanoyl radical, C2 - a C6 alkoxy carbonyl group, A dioxoranyl group, the dioxoranyl group permuted by C1 - C6 alkyl group, An OKISANIRU radical, the dioxa nil radical, the dioxa nil radical permuted by C1 - C6 alkyl group, A benzodioxa nil radical, a bicyclo [2.2.1] heptane-2-IRU radical, C1 - C6 alkylthio group, a pyrrolidinyl radical, the pyrrolidinyl radical permuted by C1 - C6 alkyl group, A piperidinyl radical, the piperidinyl radical permuted by C1 - C6 alkyl group, A morpholino radical, a 4-C2 - C6 alkoxy carbonyl piperazine-1-IRU radical, Pyrrolyl radical, pyridyl radical, N, and N-JI C1 - C6 alkylamino radical, N and N-JI C1 - C6 alkylamino C1 - C6 alkoxy group, C1 C6 alkoxy [1] C - C6 alkoxy group, "A phenoxy group and a phenyl group, C1 - C6 alkyl group, C1 - C6 alkoxy group, The phenyl group permuted by 1 of the radical chosen from a halogen atom, a phenylethyl radical, a phenoxy group, nitril, and a methylthio radical", or two pieces, it is a biphenyl radical, a phenylthio radical, a furil radical, a thienyl group, a thiazolyl radical, the thiazolyl radical permuted by C1 - C6 alkyl group, a torr IJINO radical, N-C1 - C6 alkyl torr IJINO radical, and a pyrrolidone-1-IRU radical, and A is C1 - C10 alkylene group. it is the radical shown.] It is the radical come out of and shown. It is 20-HETE production enzyme inhibitor characterized by including the imidazole derivative expressed with], or its salt permitted pharmaceutically as an active principle.
[0010]
Moreover, other this inventions are the following types (2).
[0011]
[Formula 4]

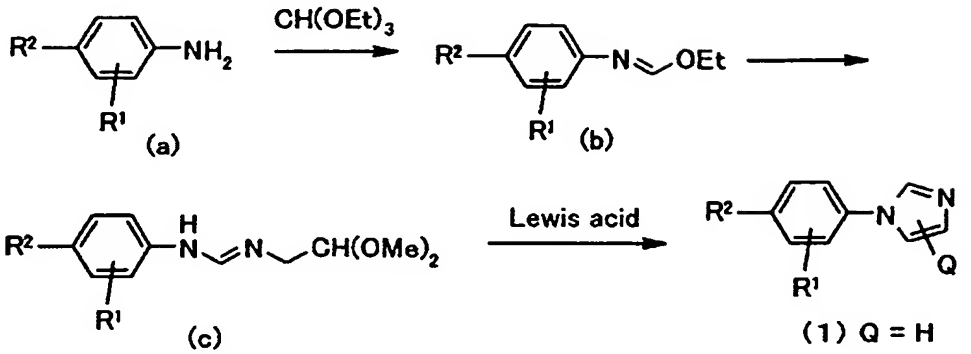


(2)

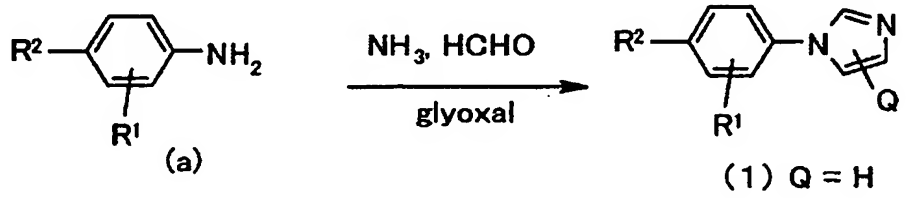
[0012]
Q' is a hydrogen atom, or C1 - C4 alkyl group among {type. R11 They are a hydrogen atom, C1 - C6 alkyl group, and a halogen atom. R12 R13 among a morpholino radical or a formula R13-O- [type C3 - C14 alkynyl group, C3 - C10 cycloalkyl radical, 1-phenyl-2-propynyl group, or formula R14-A' - (among a formula) R14 C3 - C10 cycloalkyl radical, C1 - C10 alkoxy group, C2 - C10 alkanoyl radical, a dioxoranyl group, the dioxoranyl group permuted by C1 - C6 alkyl group, An OKISANIRU radical, the dioxa nil radical, the dioxa nil radical permuted by C1 - C6 alkyl group, A benzodioxa nil radical, a bicyclo [2.2.1] heptane-2-IRU radical, C1 - C6 alkylthio group, a 4-C2 - C6 alkoxy carbonyl piperazine-1-IRU radical, it is pyrrolyl radical, N, and N-JI C1 - C6 alkylamino C1 - C6 alkoxy group, C1 C6 alkoxy [1] C - C6 alkoxy group, a furil radical, a thienyl group, and a pyrrolidone-1-IRU radical, and A' is C1 - C10 alkylene group. it is the radical shown.] It is the radical come out of and shown. The imidazole derivative expressed with} or its salt permitted pharmaceutically is offered.
[0013]
Other this inventions offer the physic which makes an active principle the above-mentioned imidazole derivative or its salt permitted pharmaceutically.
Other this inventions offer the kidney disease, cerebrovascular disease, or cardiovascular disease remedy which makes an active principle the above-mentioned imidazole derivative or its salt permitted pharmaceutically.
[0014]
The vocabulary used in this invention is defined below.
In this invention, "Cx-Cy" shows that the radical which continues after that has the carbon atom of a x-y individual.
[0015]
A halogen atom is a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom, is a fluorine atom, a chlorine atom, or a bromine atom preferably, and is a fluorine atom or a chlorine atom more preferably.
C1 - C14 alkyl group mean the alkyl group of the shape of the shape of a straight chain which has 1-14 carbon atoms, and branching, and C1 - its C8 alkyl group are desirable. As C1 - C8 alkyl group, methyl group, ethyl group, n-propyl group, n-butyl, n-hexyl group, n-heptyl radical, n-octyl radical, isobutyl radical, sec-butyl, isopentyl radical, iso hexyl group, 3-methyl heptyl radical, 3, and 3-dimethyl butyl etc. is more desirable, for example.
C3 - C10 cycloalkyl radical mean the annular alkyl group which has 3-10 carbon atoms, for example, a cyclo propyl group, cyclo butyl, a cyclopentylic group, a cyclohexyl radical, a cycloheptyl radical, a cyclo octyl radical, etc. are mentioned. Especially, a cyclo propyl group, a cyclopentylic group, and a cyclohexyl radical are desirable.
[0016]
C2 - C14 alkenyl radical mean the alkenyl radical of the shape of the shape of a straight chain which has at least one double bond and 2-14 carbon atoms, and branching. For example, an ethenyl radical, a propenyl radical, 2-butenyl group, a 3-methyl-2-butenyl group, A pentenyl radical, a 2-methyl-2-pentenyl radical, a hexenyl radical, 2, 4-hexa dienyl radical, a heptenyl radical, an octenyl group, 3, the 7-dimethyl -2, 6-OKUTA dienyl radical, etc. are mentioned.
C2 - C14 alkynyl group mean the alkynyl group of the shape of the shape of a straight chain which has at least one triple bond and 2-6 carbon atoms, and branching, for example, an ethynyl group, 2-propynyl group, a butynyl radical, 5-cutting-pliers nil radical, a hexenyl radical, a

heptynyl radical, an OKUCHINIRU radical, etc. are mentioned.
[0017]
C1 - C10 alkoxy group mean the alkoxy group of the shape of the shape of a straight chain which has 1-10 carbon atoms, and branching, and C1 - its C8 alkoxy group are desirable. As C1 - C8 alkoxy group, a methoxy group, an ethoxy radical, a propoxy group, an isopropoxy group, an n-butoxy radical, an iso butoxy radical, a tert-butoxy radical, a hexyloxy radical, a heptyloxy radical, etc. are mentioned, for example.
[0018]
C1 C6 alkoxy [1] C - C6 alkoxy group have the gestalt which C1 - C6 alkoxy group, and C1 - C6 alkoxy group compounded, and C1 C4 alkoxy [1] C - its C4 alkoxy group are desirable. Especially, a methoxyethoxy radical, n-butoxyethoxy radical, etc. are more desirable.
C2 - a C6 alkoxy carbonyl group have the gestalt which the alkoxy group of the shape of the shape of a straight chain which has 2-5 carbon atoms, and branching, and one carbonyl group (-CO-) compounded, and C2 - its C4 alkoxy carbonyl group are desirable. Especially, a methoxycarbonyl group, an ethoxycarbonyl radical, etc. are more desirable.
[0019]
A dioxoranyl group means the saturation five membered ring (dioxolane) which has two oxygen atoms as a hetero atom, and the univalent radical preferably guided except for hydrogen from the ring of 1 and 3-dioxolane.
An OKISANIRU radical has the gestalt of the saturation six membered ring which has one oxygen atom as a hetero atom, and contains 2-OKISANIRU radical and 3-OKISANIRU radical.
The dioxa nil radical means the saturation six membered ring (dioxane) which has two oxygen atoms as a hetero atom, and the univalent radical preferably guided except for hydrogen from the ring of 1 and 3-dioxane. The ring of the radical may be permuted by C1 - C6 alkyl group, for example, the dioxa nil radicals permuted by C1 - C6 alkyl group are the 5 and 5-dimethyl -1, a 3-dioxane-2-IRU radical, etc.
[0020]
C1 - C6 alkylthio group have the gestalt which the alkyl group of the shape of the shape of a straight chain which has 1-6 carbon atoms, and branching, and one thio radical (-S-) compounded, and C1 - its C4 alkylthio group are desirable. For example, a methylthio radical, an ethyl thio radical, etc. are more desirable.
[0021]
A pyrrolidinyl radical means the univalent radical guided except for a hydrogen atom from on the annular nitrogen atom of a pyrrolidine, or a carbon atom, for example, 1-pyrrolidinyl radical, 2-pyrrolidinyl radical, 3-pyrrolidinyl radical, etc. are mentioned. the pyrrolidinyl radical permuted by C1 - C6 alkyl group -- at least one hydrogen atom on the radical -- C1-C -- 6 alkyl group, it is the pyrrolidinyl radical preferably permuted by C1 - C4 alkyl group, for example, an N-methyl pyrrolidine-2-IRU radical etc. is mentioned.
A piperidinyl radical means the univalent radical guided except for a hydrogen atom from on the carbon atom of a piperidine. The piperidinyl radical permuted by C1 - C6 alkyl group is a piperidinyl radical by which the nitrogen atom of the radical was permuted by C1 - C6 alkyl group, for example, an N-methyl piperidine-2-IRU radical, an N-methyl piperidine-3-IRU radical, etc. are mentioned.
The nitrogen atom of the 4th place of a piperazine is embellished with C2 - a C6 alkoxy carbonyl group, and a 4-C2 - C6 alkoxy carbonyl piperazine-1-IRU radical means the univalent radical guided except for a hydrogen atom from on [of the 1st place] a nitrogen atom.
A morpholino radical means the univalent radical guided except for a hydrogen atom from on the nitrogen atom of a morpholine.
[0022]
A furil radical contains 2-furil radical and 3-furil radical.
A thienyl group contains 2-CHIENIRURU radical and 3-thienyl group.
A thiazolyl radical contains 2-thiazolyl radical, 4-thiazolyl radical, and 5-thiazolyl radical. moreover, the thiazolyl radical permuted by C1 - C6 alkyl group -- at least one hydrogen atom on the ring -- C1 - C6 alkyl -- desirable -- C1-C -- 4 alkyl group, it is the thiazolyl radical

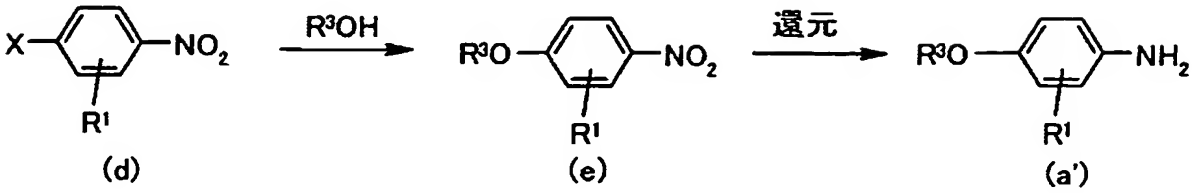
more preferably permuted by the methyl group, for example, a 4-methyl thiazole-5-IRU radical etc. is mentioned.
A pyridyl radical contains 2-pyridyl radical, 3-pyridyl radical, and 4-pyridyl radical. A pyrrolyl radical has desirable 1-pyrrolyl radical (N-pyrrolyl radical) including 1-pyrrolyl radical, 2-pyrrolyl radical, and 3-pyrrolyl radical.
[0023]
N and N-JI C1 - C6 alkylamino C1 - C6 alkoxy group have the gestalt which N and N-JI C1 - C6 alkylamino radical, and C1 - C6 alkoxy group compounded, and N and N-diethylaminoethoxy radical etc. is mentioned.
A pyrrolidone-1-IRU radical contains a 2-pyrrolidone-1-IRU radical and a 3-pyrrolidone-1-IRU radical.
[0024]
C1 defined by A and A' - C10 alkylene group mean the alkylene group of the shape of the shape of a straight chain which has 1-10 carbon atoms, and branching, for example, methylene group, methyl methylene group, ethylene, propylene radical, heptylene radical, 2, and 2-dimethyl propylene radical, a hexylene radical, etc. are mentioned.
[0025]
Various kinds of above-mentioned radicals and besides the permuted gestalt which was mentioned above At least one hydrogen atom on the radical For example, a fluorine atom, a chlorine atom, Halogen atom; nitro group; amino-group; hydroxy group; thiol group; formyl group; carboxyl group; cyano group; carbamoyl groups, such as a bromine atom and an iodine atom; A methyl group, An ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, Alkyl groups, such as a neopentyl radical and a tert-pentyl radical; A phenyl group, Aryl groups, such as a naphthyl group, a biphenyl radical, and an anthranil; A pyrrolyl radical, Alkoxy carbonyl groups, such as heterocycle radical; methoxycarbonyl groups, such as a pyridyl radical and a thienyl group, and an ethoxycarbonyl radical; An acetyl group, Acyl groups, such as benzoyl; a non-hydrogen atom or radicals, such as alkoxy group; methylthio radicals, such as a methoxy group, an ethoxy radical, and a propoxy group, an ethyl thio radical, and a propyl thio radical, may permute. [, such as alkylthio group;,] In addition, the carbon atomic number in these substituents is not contained in above-mentioned x or y.
[0026]
With the salt permitted pharmaceutically, moreover, alkaline metals and alkaline earth metal, It is a salt with a salt with ammonium, alkylammonium, etc., a mineral acid, or an organic acid. For example, sodium salt, potassium salt, a calcium salt, ammonium salt, An aluminum salt, triethyl ammonium salt, acetate, propionate, Butyrate, a formic acid salt, a trifluoroacetic acid salt, a maleate, a tartrate, citrate, A stearate, succinate, ethyl succinate, a salt lactobionate, Gluconate, glucoheptonate, a benzoate, a methansulfonic acid salt, An ethane-sulfonic-acid salt, a 2-hydroxy ethane-sulfonic-acid salt, a benzenesulfonic acid salt, A Para toluenesulfonic acid salt, a lauryl sulfate, malate, an aspartic-acid salt, Glutamate, adipate, a salt with a cysteine, a salt with N-acetylcysteine, A hydrochloride, the hydrobromate, phosphate, a sulfate, an iodine hydro acid salt, a nicotinic-acid salt, an oxalate, a picrate, a thiocyanate, an undecanoic acid salt, a salt with an acrylic-acid polymer, a salt with a carboxyvinyl polymer, etc. can be mentioned.
[0027]
[Embodiment of the Invention]
this invention compound (1) is compoundable by the approach shown below.
[0028]
[Formula 5]



[0029]
Manufacturing method 1; An aniline derivative (a) is made for J.Heterocyclic Chem., the 25th volume, and the 1649th term (1988) to react to reference with ORUTOGI acid ester, such as ORUTOGI acid TORIMECHIRU and a triethyl orthoformate, under existence of the acid catalyst of an acetic acid or a hydrochloric acid, or nonexistence, and a imino ether derivative (b) is obtained. 150 degrees C of reaction temperature of reaction time are 2 - 72 hours at 70-100 degrees C preferably from a room temperature. Next, a imino ether derivative (b) is made to react with the suitable amino acetaldehyde dimethyl acetal in a solvent (a methanol, ethanol, propanol, a tetrahydrofuran, dioxane, toluene, a methylene chloride, chloroform, an acetonitrile, ethyl acetate, dimethyl sulfoxide, dimethylformamide, etc.), and a formamidine derivative (c) is obtained. the reaction temperature at this time -- room temperature - it is 70-100 degrees C preferably, and 150 degrees C of reaction time are 2 - 24 hours. Next, a formamidine derivative (c) can be made to be able to react into a suitable solvent under coexistence of Lewis acid or acid catalysts (a titanium tetrachloride, trifluoro borane etherate, acetic acid, etc.) (the ether, a tetrahydrofuran, dimethoxyethane, dioxane, etc.), and this invention compound (1) can be compounded (it is synonymous with the above the inside R1 and R2 of a formula). Moreover, it can also lead to other this invention compounds (1) by changing mutually R2 of this invention compound (1) compounded by this approach.
[0030]
[Formula 6]

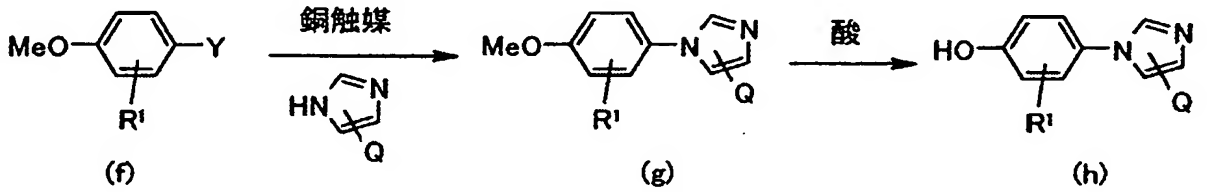


[0031]
Manufacturing method 2; a compound (1) is also directly compoundable from an aniline derivative (a). namely, an aniline derivative, ammonia, formaldehyde, and a glyoxal -- the ratio of 1:1:1:1 -- mixing -- the inside of the mixed solvent of water, or alcohol/water -- reaction temperature -- room temperature - 150 degrees C (1) of this invention compounds are compoundable by reacting at 70-120 degrees C preferably (it is synonymous with the above the inside R1 and R2 of a formula).
[0032]
[Formula 7]



(d) (e) (a')

[0033]
Manufacturing method 3; it is the following, and the aniline derivative (a') (R2 shows a permutation alkoxy group, i.e., R2=R3O) which is synthetic intermediate field can be made and compounded. Namely, a nitrobenzene derivative (d) (leaving groups, such as a fluorine and chlorine, are shown by the inside X of a formula) other notations — the above — being synonymous — the inside of a suitable solvent (a methanol and ethanol —) Propanol, a tetrahydrofuran, dioxane, toluene, a methylene chloride, Chloroform, an acetonitrile, ethyl acetate, dimethyl sulfoxide, need, such as dimethylformamide, — responding — a base (triethylamine, N, and N-diisopropyl ethylamine —) It can react with various corresponding alcohols under existence of a pyridine, potassium carbonate, a calcium carbonate, cesium carbonate, sodium hydride, sodium methoxide, a t-butoxy potassium, etc., and a compound (e) can be manufactured. At this time, 0 degree C - 80 degrees C of reaction temperature are 0 degree C - a room temperature preferably, and reaction time is 1 - 2 hours preferably for 1 to 12 hours. next, a compound (e) — the inside of a suitable solvent (a methanol, ethanol, and propanol —) A tetrahydrofuran, dioxane, toluene, a methylene chloride, chloroform, Reducing agents, such as an acetonitrile and ethyl acetate (under palladium activated carbon / hydrogen ambient atmosphere) Palladium activated carbon / hydrazine hydrate, palladium activated carbon / ammonium formate, Tin(II) chloride 1 hydrate, iron/ammonium chloride, a Raney nickel catalyst / hydrazine hydrate, etc. can manufacture an aniline derivative (a') by returning a nitro group using the bottom of palladium activated carbon / hydrogen ambient atmosphere preferably. reaction temperature — room temperature - it is room temperature -100 degree C preferably, and 150 degrees C of reaction time are 1 hour - 24 hours.
[0034]
[Formula 8]



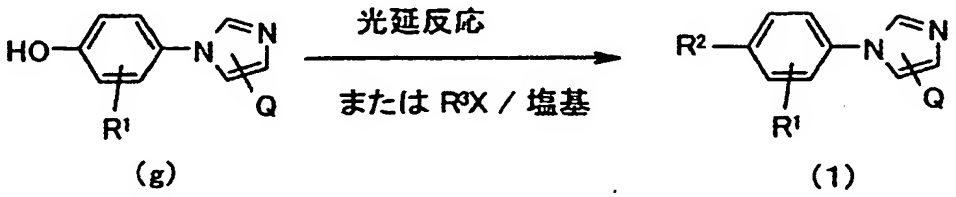
(f) (g) (h)

[0035]
Manufacturing method 4; through intermediate field (h), a compound (1) is the following, and can be made and manufactured. A phenyl boron acid or a halogenation phenyl derivative (f) (the inside Y of a formula expresses B(OH)2 or a halogen atom) other notations — the above — being synonymous — the inside of a suitable solvent (a methanol and ethanol —) Propanol, a tetrahydrofuran, dioxane, toluene, a methylene chloride, Chloroform, an acetonitrile, ethyl acetate, dimethyl sulfoxide, By dimethylformamide etc., under copper catalyst ([Cu(OH) TMEDA] 2Cl2, 2b(CuOTf) enzene, etc.) existence, It condenses with an imidazole derivative under an oxygen ambient atmosphere preferably, and intermediate field (g) can be manufactured [Organic Lett., the 2nd volume, and the 1237th term (2000)]. The room temperature of reaction temperature is desirable and reaction time is 12 - 24 hours. Subsequently, intermediate field (g) can be reacted at 100 degrees C - 150 degrees C among 48% hydrogen bromide, and an

intermediate-field compound (h) can be manufactured. Reaction time is 12 hours - 24 hours preferably for 12 hours to 72 hours.

[0036]

[Formula 9]



[0037]

Next, 4 -(imidazole-1-IRU)- The Mitsunobu reaction (Org.Reactions, the 42nd volume, the 335th term) can be used, and a phenol derivative (h) and various corresponding alcohol can be manufactured. A compound (h) namely, in suitable solvents (a tetrahydrofuran, dioxane, toluene, a methylene chloride, chloroform, an acetonitrile, ethyl acetate, dimethyl sulfoxide, dimethylformamide, etc.) A phosphine reagent (triphenyl phosphine, tributyl phosphine, a diphenyl-2-pyridyl phosphine, etc.), diazo reagent (a diethyl azo dicarboxy rate, G tert-butyl azo dicarboxy rate, etc.) and various corresponding alcohols -- 0 degree C - a room temperature -- desirable -- a room temperature -- 2 - 12 hours -- reacting -- this invention compound (1) (the notations in a formula are the above and this meaning.) It can manufacture. Or various alkyl halides (R3X and X express a halogen and other notations are synonymous with the above) a suitable solvent (an acetone, dimethylformamide, and a tetrahydrofuran --) inside, such as the ether, -- a suitable base (triethylamine, N; and N-diisopropyl ethylamine --) It comes out under existence of a pyridine, potassium carbonate, a calcium carbonate, cesium carbonate, sodium hydride, sodium methoxide, a t-butoxy potassium, etc. It can react at a room temperature preferably for 2 to 24 hours, and the 0-degree-C - room temperature, and this invention compound (1) whose R2 is R3O can be manufactured.

[0038]

Taking orally or a parenteral target can be medicated with this invention compound and its salt permitted pharmaceutically. The administration pharmaceutical form is a tablet, a capsule, a granule, powder, powder material, the trochiscus, an ointment, cream pharmaceuticals, an emulsion, suspension, suppositories, injections, etc., and can manufacture all with the pharmaceutical preparation technique (for example, the approach of specifying to the 14th amendment Japanese pharmacopoeia) of common use. These administration pharmaceutical forms can be suitably chosen according to a patient's symptom, age, and the purpose of a therapy. In manufacture of the pharmaceutical preparation of various pharmaceutical forms, excipients (for example, crystalline cellulose, starch, a lactose, a mannitol, etc.) in ordinary use, a binder, lubricant (for example, hydroxypropylcellulose, a polyvinyl pyrrolidone, etc.) (for example, magnesium stearate, talc, etc.), disintegrator (for example, carboxymethyl-cellulose calcium etc.), etc. can be used.

[0039]

The dose of the salt permitted pharmaceutically is 1-2000mg per day in the case where an adult is treated, and medicates the compound list concerning this invention with this in 1 time per or several steps day. This dose can be suitably fluctuated according to a patient's age, weight, and symptom.

[0040]

[Effect of the Invention]

The compound concerning this invention and its salt permitted pharmaceutically have the outstanding 20-HETE production inhibitory action, and is excellent also like physical properties, such as solubility. Therefore, the compound concerning this invention is useful as the illness with which 20-HETE in Homo sapiens and an animal is concerned, for example, various kidney

disease, the cerebrovascular disease, and various cardiovascular disease remedies.
[0041]
[Example]
Hereafter, an example is given and this invention is explained in more detail.
Example 1
Manufacture of a 1-[4-propyl phenyl]-imidazole hydrochloric acid (compound 108)
4-propyl aniline (2.03g, 0.0150 mols) Triethyl orthoformate (4.99g, 0.337 mols) Mixture was stirred at 100 degrees C for 7 hours. After cooling to a room temperature, it is a methanol to reaction mixture. (15mL) The amino acetaldehyde dimethyl acetal (5.69g, 0.0541 mols) was added, and it stirred at the room temperature for 30 minutes, and stirred at 100 more degrees C for 4 hours. They are dimethoxyethane (20mL) and a 1M titanium-tetrachloride-toluene solution to the residue which condensed reaction mixture and was obtained after cooling to a room temperature. (21mL, 0.021 mols) In addition, it stirred under heating reflux further at the room temperature for 4 hours for 1 hour. After cooling to a room temperature, the sodium-hydroxide water solution was added to reaction mixture, and chloroform extracted. The organic layer was dried and condensed with magnesium sulfate. A silica gel chromatography (chloroform-methanol = 97:3) refines the obtained residue, and it is a 1-[4-propyl phenyl]-imidazole. (2.0g) It obtained as brown oily matter. A 4-N hydrochloric-acid-ethyl-acetate solution is added to a product, and it recrystallizes [mixed solvent / of ethyl-acetate-chloroform], and is an end of non-color powder-like title compound. (1.38g, 41.2%) It obtained. The 155.5 to 157.0 degree C melting point
[0042]
Example 2
Manufacture of [2-[2-(4-imidazole-1-IRU-phenoxy)-ethoxy]-ethyl]-dimethylamine 2 hydrochloric acid (compound 116)
Sodium hydride (60% oil, 1.0 g, 0.26 mols) Dimethylformamide (3.0ml) Bottom of ice-cooling to suspension, N, and N-dimethylamino ethyloxy ethanol (2.3g, 0.26 mols) Dimethylformamide solution (5ml) It was dropped and stirred for 10 minutes. It is 4-fluoro nitrobenzene to this reaction mixture. (3g, 0.021 mols) Dimethylformamide solution (10mL) It was dropped and stirred at the room temperature for 2 hours. Water is added to a reaction mixture, ethyl acetate extracts, after saturation brine washing, it dries MgSO4, an organic layer is condensed under reduced pressure, and it is a dimethyl-[2-[2-(4-nitro phenoxy)-ethoxy]-ethyl] amine. (5.9g) It obtained. It is a methanol about the compound obtained above. (100mL) It dissolves and is 10% palladium activated carbon. (0.6g) In addition, it stirred at the room temperature under the hydrogen ambient atmosphere for 3 hours. After checking disappearance of a raw material by TLC analysis, cerite is used, insoluble matter is filtered, filtrate is condensed, and it is an aniline derivative. (5.0g) It obtained as brown oily matter. Next, it is a triethyl orthoformate to this aniline derivative. (10mL, 0.060 mols) In addition, it stirred at 100 degrees C for 20 hours. After cooling to a room temperature, they are a methanol (80mL) and an amino acetaldehyde dimethyl acetal to reaction mixture. (6.8mL, 0.063 mols) In addition, it stirred at 100 degrees C for 1.5 hours. It is dimethoxyethane to the residue which condensed reaction mixture and was obtained. (30mL) 1M titanium-tetrachloride-toluene solution (25mL, 0.025 mols) In addition, it stirred under heating reflux for 5 hours. After cooling to a room temperature, the sodium-hydroxide water solution was added to reaction mixture. After filtering the insoluble matter which deposited, ethyl acetate extracted filtrate. The organic layer was dried and condensed with magnesium sulfate after saturation brine washing. NH mold silica gel chromatography (hexane-ethyl acetate = 1:2) refines the obtained residue. [2-[2-(4-imidazole-1-IRU-phenoxy)-ethoxy]-ethyl]-dimethylamine (0.40g, 6.9%) was obtained as oily matter. The product was dissolved in the ether, the powder which added the 4M hydrochloric-acid-ethyl-acetate solution, condensed, and deposited was washed with ethyl acetate, and the title compound was obtained. (428mg) . The 174.0 to 179.0 degree C melting point
[0043]
Example 3
Manufacture of 1-[4-propyloxy phenyl]-imidazole toluenesulfonate (compound 94)
4-(imidazole-1-IRU) phenol (1.0g, 6.25mmol) Propanol (563mg, 9.38mmol) Triphenyl phosphine

(2.46g, 9.38mmol) And tetrahydrofuran (20mL) The diethyl azo dicarboxy rate (1.48mL, 9.38mmol) was applied to mixture, and it stirred at the room temperature for 6 hours. After condensing a reaction mixture, ethyl acetate (40mL) was added and 1M hydrochloric acid (20mL) extracted. Ethyl acetate extracted, after neutralizing a water layer by 5M sodium hydroxide. The organic layer was dried and condensed with magnesium sulfate after saturation brine washing. NH mold silica gel chromatography (hexane-ethyl acetate = 1:2) refines the obtained residue, and it is a 1-[4-propyloxy phenyl]-1H-imidazole. (1.17g, 92%) It obtained as colorless oily matter. This is dissolved in ethanol and it is p-toluenesulfonic acid monohydrate. (1.1g, 5.78mmol) The crystal which added the ethanol solution and deposited is filtered and it is an end of non-color powder-like title compound. (1.98g, 85%) It obtained. The 148.0 to 150.0 degree C melting point

[0044]

Example 4

Manufacture of 1-[4-butoxy phenyl]-2-methylimidazole toluenesulfonate (compound 117)

(1) 4-methoxypheny borate (3.7g, 24.4mmol) 1-H-2-methylimidazole (1.0g, 12.2mmol) Methylene chloride (48mL) [Cu(OH) TMEDA]2Cl2 (g [0.57], 1.22mmol) was added to mixture, and it stirred at the room temperature under the oxygen ambient atmosphere for 18 hours. Filtrate was condensed, after filtering the reaction mixture and removing insoluble matter. NH mold silica gel chromatography (hexane-ethyl acetate = 4:1) refines the obtained residue, and it is 1-[4-methoxypheny]-2-methylimidazole. (2.35g) It obtained.

[0045]

(2) 1-[4-methoxypheny]-2-methylimidazole (2.0g) 48% hydrogen bromide (20mL) Mixture was reacted at 100 degrees C for 16 hours. The crystal which deposited after neutralization by 6M sodium hydroxide after cooling reaction mixture to a room temperature is filtered, and it is 4-(2-methylimidazole-1-IRU) phenol. (0.75g, 40%) It obtained.

[0046]

(3) 4-(2-methylimidazole-1-IRU) phenol (0.20g, 1.2mmol) Dimethylformamide (2mL) To a solution, it is 1-IODO-n-butane. (0.25g, 1.38mmol) Potassium carbonate (0.19g, 1.38mmol) In addition, it stirred at the room temperature for 64 hours. Water was added to reaction mixture and the mixed solvent of hexane-ethyl-acetate =1:1 extracted. The organic layer was dried and condensed with magnesium sulfate after washing with saturation brine. NH mold silica gel chromatography (hexane-ethyl acetate = 4:1) refines the obtained residue, and it is 1-[4-butoxy phenyl]-2-methylimidazole. (0.17g, 64%) It obtained. The crystal which dissolved this in ethanol, added the ethanol solution of p-toluenesulfonic acid monohydrate, and deposited is filtered, and it is an end of non-color powder-like title compound. (0.18g, 39%) It obtained. The 148.0 to 149.0 degree C melting point

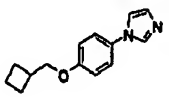
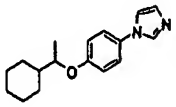
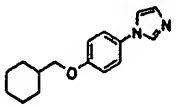
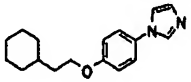
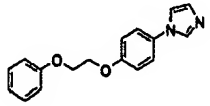
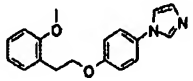
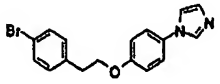
[0047]

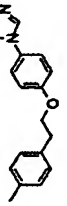
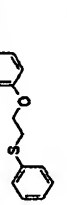
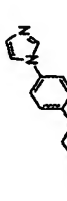
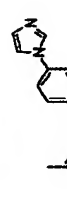
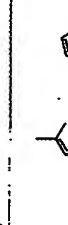
The compound shown in Table 1 was compounded by performing the same reaction actuation as examples 1-4 using the start raw material which corresponds respectively. In addition, in Table 1, the compound compounded in the examples 1-4 was marked collectively.

[0048]

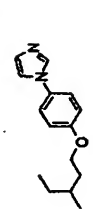
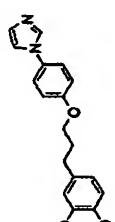
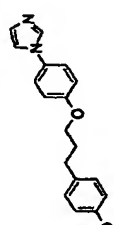
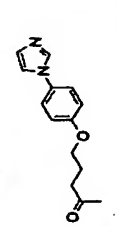
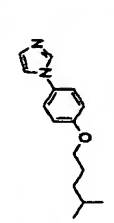
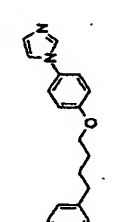
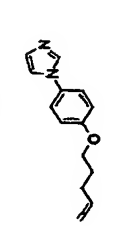
[Table 1]

[0049]
[Table 2]

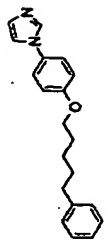
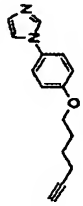
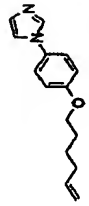
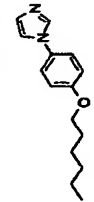
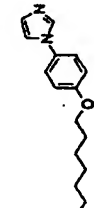
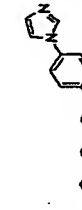
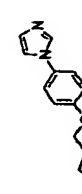
化合物番号	構造式	^{1}H NMR (300MHz, $CDCl_3$) spectra and melting points	抑制率 % at 0.1uM	IC_{50} (nM)
化合物1		δ 1.86-2.04 (m, 4H), 2.15 (m, 2H), 2.79 (m, 1H), 3.96 (d, J = 6.7Hz, 2H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	85.8	
化合物2		δ 1.03-1.22 (m, 4H), 1.27 (d, J = 6.1Hz, 3H), 1.58-1.80 (m, 6H), 1.93 (m, 1H), 4.15 (d, J = 6.1Hz, 1H), 6.95 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	79.6	
化合物3		δ 1.04-1.19 (m, 2H), 1.20-1.39 (m, 3H), 1.62-1.92 (m, 6H), 3.78 (d, J = 6.2Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	84.4	
化合物4		δ 1.00 (m, 2H), 1.19-1.38 (m, 3H), 1.45-1.80 (m, 8H), 4.03 (t, J = 6.7Hz, 2H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	94.1	
化合物5		δ 4.37 (s, 4H), 6.95-6.98 (m, 3H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.22 (s, 1H), 7.26-7.33 (m, 3H), 7.77 (s, 1H).	96.9	
化合物6		δ 3.14 (t, J = 7.5Hz, 2H), 3.86 (s, 3H), 4.19 (t, J = 7.5Hz, 2H), 6.88-6.95 (m, 2H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.18-7.13 (m, 6H), 7.76 (s, 1H).	97.3	
化合物7		δ 3.07 (t, J = 6.7Hz, 2H), 4.18 (t, J = 6.7Hz, 2H), 6.96 (m, J_{AB} = 9.0Hz, 2H), 7.16-7.20 (m, 4H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.45 (m, J_{AB} = 8.2Hz, 2H), 7.75 (s, 1H).	100.8	

化合物 8		δ 2.34 (s, 3H), 3.09 (t, J = 7.1Hz, 2H), 4.18 (t, J = 7.1Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.13-7.20 (m, 4H), 7.27 (m, J_{AB} = 9.0Hz, 2H), 7.75 (s, 1H).	105.9
化合物 9		δ 3.32 (t, J = 6.9Hz, 2H), 4.18 (t, J = 6.9Hz, 2H), 6.93 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.19 (s, 1H), 7.21-7.35 (m, 5H), 7.43 (m, J_{AB} = 9.0Hz, 2H), 7.75 (s, 1H).	99.0
化合物 10		δ 2.56 (t, J = 2.5Hz, 1H), 4.75 (d, J = 2.5Hz, 2H), 7.08 (m, J_{AB} = 9.0Hz, 2H), 7.10 (s, 1H), 7.19 (s, 1H), 7.33 (m, J_{AB} = 9.0Hz, 2H), 7.77 (s, 1H).	42.9
化合物 11		δ 1.77 (s, 3H), 1.82 (s, 3H), 4.55 (d, J = 6.7Hz, 2H), 5.50 (m, 1H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	93.8
化合物 12		δ 1.62 (s, 3H), 1.69 (s, 3H), 1.82 (s, 3H), 2.15 (m, 4H), 4.54 (d, J = 6.8Hz, 2H), 5.12 (m, 1H), 5.51 (t, J = 6.8Hz, 1H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	91.9
化合物 13		δ 1.78 (dd, J = 1.4, 6.2Hz, 3H), 4.50 (dt, J = 1.2, 5.9Hz, 2H), 5.69-5.96 (m, 2H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	104.9
化合物 14		δ 1.78 (d, J = 6.8Hz, 3H), 4.58 (d, J = 6.2Hz, 2H), 5.73-5.81 (m, 2H), 6.10 (m, 1H), 6.35 (dd, J = 10.7, 15.7Hz, 3H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	98.1

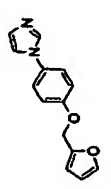
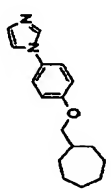
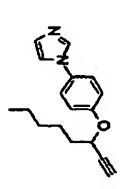
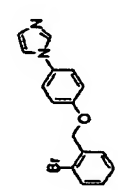
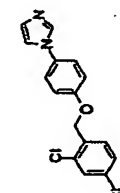
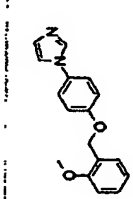
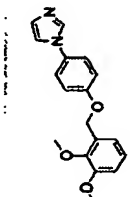
[0050]
[Table 3]

化合物 15		δ 0.92 (d, J = 7.5Hz, 3H), 0.96 (d, J = 6.4Hz, 3H), 1.26 (m, 1H), 1.40 (m, 1H), 1.62 (m, 2H), 1.84 (m, 1H), 4.02 (m, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	104.0
化合物 16		δ 2.11 (tt, J = 6.2, 7.2Hz, 2H), 2.78 (t, J = 7.2Hz, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 3.99 (t, J = 6.2Hz, 2H), 6.74-6.82 (m, 3H), 6.85 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	97.4
化合物 17		δ 2.10 (tt, J = 6.4, 7.2Hz, 2H), 2.77 (t, J = 7.2Hz, 2H), 3.78 (s, 3H), 3.98 (t, J = 6.4Hz, 2H), 6.85 (m, J_{AB} = 8.5Hz, 2H), 6.96 (m, J_{AB} = 9.0Hz, 2H), 7.13 (m, J_{AB} = 8.5Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	99.5
化合物 18		δ 2.09 (tt, J = 6.1, 7.2Hz, 2H), 2.19 (s, 3H), 2.68 (t, J = 7.2Hz, 2H), 4.02 (t, J = 6.1Hz, 2H), 6.96 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	105.4
化合物 19		δ 0.94 (d, J = 6.5Hz, 6H), 1.37 (m, 2H), 1.63 (m, 2H), 1.81 (m, 2H), 3.98 (t, J = 6.5Hz, 2H), 6.98 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	85.7
化合物 20		δ 1.80-1.90 (m, 4H), 2.71 (t, J = 7.1Hz, 2H), 4.00 (t, J = 6.1Hz, 2H), 6.95 (m, J_{AB} = 9.0Hz, 2H), 7.18-7.32 (m, 9H), 7.76 (s, 1H).	94.0
化合物 21		δ 1.91 (m, 2H), 2.25 (m, 2H), 4.01 (t, J = 6.4Hz, 2H), 5.01-5.12 (m, 2H), 5.85 (m, 1H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	99.2

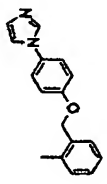
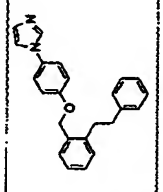
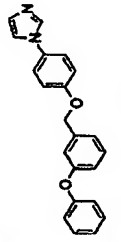
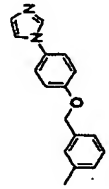
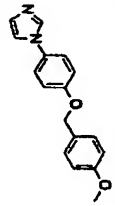
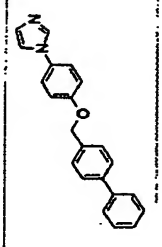
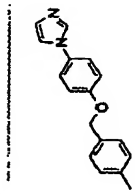
[0051]
[Table 4]

化合物 22		δ 1.47-1.89 (m, 6H), 2.66 (t, J = 7.5Hz, 2H), 3.98 (t, J = 6.5Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.18-7.20 (m, 5H), 7.26-7.31 (m, 4H), 7.76 (s, 1H).	88.5
化合物 23		δ 1.74 (m, 2H), 1.92 (m, 2H), 1.98 (t, J = 2.6Hz, 2H), 2.30 (dt, J = 2.8, 7.0Hz, 2H), 4.03 (t, J = 6.3Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	99.5
化合物 24		δ 1.60 (m, 2H), 1.83 (quint, J = 7.0Hz, 2H), 2.14 (q, J = 7.0Hz, 2H), 4.00 (t, J = 6.5Hz, 2H), 4.98-5.08 (m, 2H), 5.77-5.91 (m, 1H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	99.1
化合物 25		δ 0.92 (t, J = 7.0Hz, 3H), 1.33-1.39 (m, 4H), 1.47 (m, 2H), 1.81 (m, 2H), 3.99 (t, J = 6.7Hz, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	98.6
化合物 26		δ 0.90 (t, J = 6.8Hz, 3H), 1.25-1.45 (m, 8H), 1.81 (quint, J = 6.8Hz, 2H), 3.99 (t, J = 6.8Hz, 2H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	91.5
化合物 27		δ 0.89 (t, J = 6.8Hz, 3H), 1.23-1.54 (m, 10H), 1.79 (quint, J = 6.8Hz, 2H), 3.99 (t, J = 6.8Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	68.0
化合物 28		δ 3.89 (m, 1H), 3.99-4.18 (m, 3H), 4.46 (dt, J = 5.5, 7.7Hz, 2H), 4.95 (s, 1H), 5.11 (s, 1H), 7.01 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.31 (m, J_{AB} = 9.0Hz, 2H), 7.77 (s, 1H).	80.3

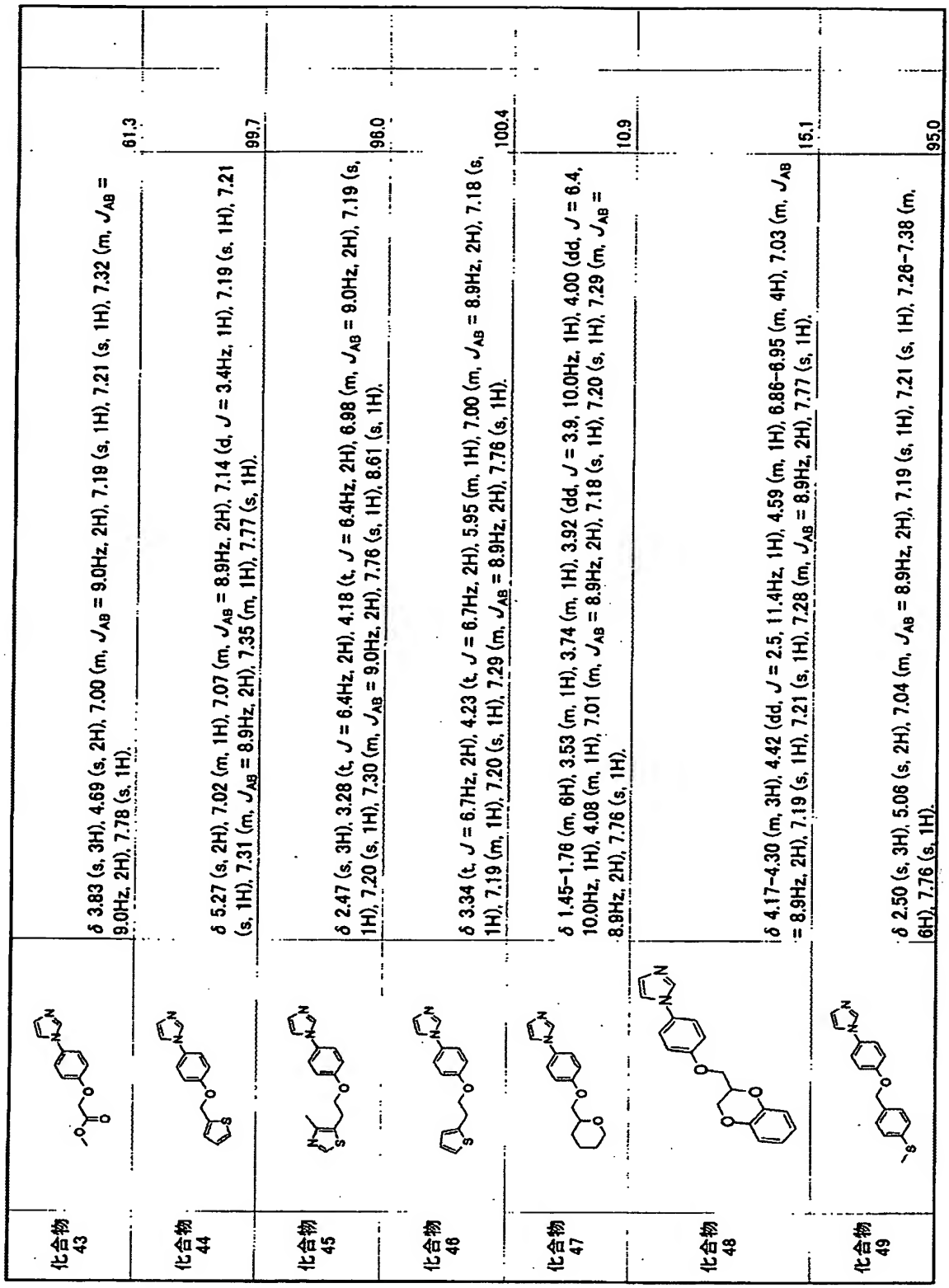
[0052]
[Table 5]

化合物 29		δ 5.05 (s, 2H), 6.40 (dd, J = 1.9, 3.1Hz, 1H), 6.47 (d, J = 3.1Hz, 1H), 7.07 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 9.0Hz, 2H), 7.48 (d, J = 1.9Hz, 1H), 7.77 (s, 1H).	64.1
化合物 30		δ 1.26-2.03 (m, 13H), 3.76 (d, J = 6.5Hz, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	102.2
化合物 31		δ 0.92 (t, J = 7.0Hz, 3H), 1.26-1.39 (m, 4H), 1.59 (m, 2H), 1.97 (m, 2H), 4.74 (m, 1H), 7.11 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 9.0Hz, 2H), 7.77 (s, 1H).	87.1
化合物 32		δ 5.18 (s, 2H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.28 (m, 1H), 7.32 (m, J_{AB} = 8.9Hz, 2H), 7.36 (m, 1H), 7.74 (d, J = 7.6Hz, 1H), 7.60 (d, J = 7.9Hz, 1H), 7.77 (s, 1H).	108.3
化合物 33		δ 5.17 (s, 2H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.26-7.35 (m, 3H), 7.45-7.52 (m, 2H), 7.77 (s, 1H).	106.6
化合物 34		δ 3.88 (s, 3H), 5.16 (s, 2H), 6.93 (d, J = 8.4Hz, 1H), 6.99 (d, J = 7.3Hz, 1H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28-7.35 (m, 3H), 7.44 (d, J = 7.3Hz, 1H), 7.76 (s, 1H).	108.9
化合物 35		δ 3.90 (s, 6H), 5.16 (s, 2H), 6.83 (dd, J = 2.3, 7.5Hz, 1H), 7.04-7.13 (m, 4H), 7.18 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	97.2

[0053]
[Table 6]

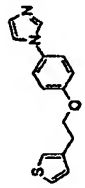
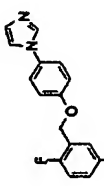
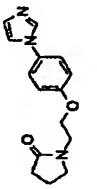
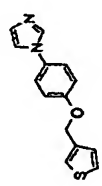
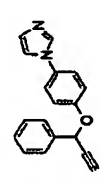
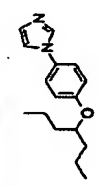
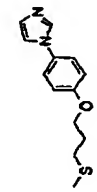
化合物 36		δ 2.40 (s, 3H), 5.08 (s, 2H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.23-7.33 (m, 5H), 7.41 (d, J = 7.3Hz, 1H), 7.77 (s, 1H).	100.5
化合物 37		δ 2.92-3.03 (m, 4H), 4.98 (s, 2H), 7.02 (m, J_{AB} = 8.9Hz, 2H), 7.12-7.36 (m, 10H), 7.41 (d, J = 7.8Hz, 1H), 7.77 (s, 1H).	83.5
化合物 38		δ 5.08 (s, 2H), 6.96-7.05 (m, 5H), 7.10-7.20 (m, 5H), 7.26-7.39 (m, 5H), 7.76 (s, 1H).	90.2
化合物 39		δ 2.39 (s, 3H), 5.07 (s, 2H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.15-7.32 (m, 8H), 7.76 (s, 1H).	110.6
化合物 40		δ 3.83 (s, 3H), 5.03 (s, 2H), 6.93 (m, J_{AB} = 8.7Hz, 2H), 7.04 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.37 (m, J_{AB} = 8.7Hz, 1H), 7.76 (s, 1H).	101.9
化合物 41		δ 5.18 (s, 2H), 7.08 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 8.9Hz, 2H), 7.32-7.65 (m, 9H), 7.77 (s, 1H).	87.0
化合物 42		δ 2.37 (s, 3H), 5.07 (s, 2H), 7.04 (m, J_{AB} = 8.7Hz, 2H), 7.19-7.23 (m, 4H), 7.26-7.35 (m, 4H), 7.78 (s, 1H).	97.3

[0054]
[Table 7]

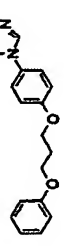
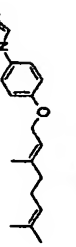
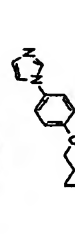
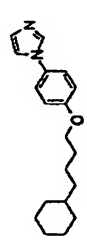
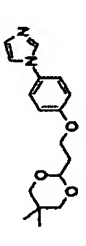
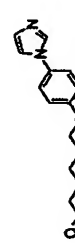
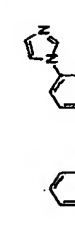


化合物 43		δ 3.83 (s, 3H), 4.69 (s, 2H), 7.00 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.32 (m, J_{AB} = 9.0Hz, 2H), 7.78 (s, 1H).	61.3
化合物 44		δ 5.27 (s, 2H), 7.02 (m, 1H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.14 (d, J = 3.4Hz, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 8.9Hz, 2H), 7.35 (m, 1H), 7.77 (s, 1H).	99.7
化合物 45		δ 2.47 (s, 3H), 3.28 (t, J = 6.4Hz, 2H), 4.18 (t, J = 6.4Hz, 2H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H), 8.61 (s, 1H).	96.0
化合物 46		δ 3.34 (t, J = 6.7Hz, 2H), 4.23 (t, J = 6.7Hz, 2H), 5.95 (m, 1H), 7.00 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.19 (m, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	100.4
化合物 47		δ 1.45-1.76 (m, 6H), 3.53 (m, 1H), 3.74 (m, 1H), 3.92 (dd, J = 3.9, 10.0Hz, 1H), 4.00 (dd, J = 6.4, 10.0Hz, 1H), 4.08 (m, 1H), 7.01 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	10.9
化合物 48		δ 4.17-4.30 (m, 3H), 4.42 (dd, J = 2.5, 11.4Hz, 1H), 4.59 (m, 1H), 6.86-6.95 (m, 4H), 7.03 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.77 (s, 1H).	15.1
化合物 49		δ 2.50 (s, 3H), 5.06 (s, 2H), 7.04 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.26-7.38 (m, 6H), 7.76 (s, 1H).	95.0

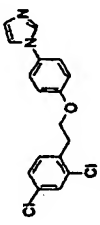
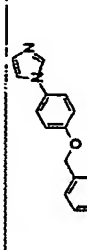
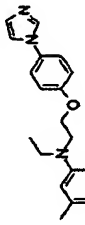
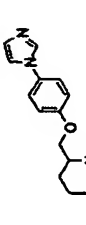
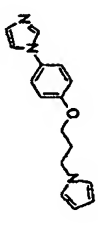
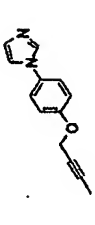
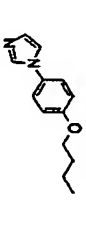
[0055]
[Table 8]

化合物 50		δ 3.16 (t, J = 6.8Hz, 2H), 4.21 (t, J = 6.8Hz, 2H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.05 (m, 1H), 7.10 (m, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.26-7.32 (m, 3H), 7.76 (s, 1H).	108.7
化合物 51		δ 5.15 (s, 2H), 6.89-7.11 (m, 4H), 7.19 (m, 3H), 7.30-7.49 (m, 2H), 7.77 (s, 1H).	102.8
化合物 52		δ 2.05 (m, 2H), 2.41 (t, J = 8.1Hz, 2H), 3.60 (t, J = 7.0Hz, 2H), 3.71 (t, J = 5.2Hz, 2H), 4.15 (t, J = 5.2Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.21 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	95.7
化合物 53		δ 5.12 (s, 2H), 7.04 (m, 8.8Hz, 2H), 7.16-7.21 (m, 3H), 7.26-7.39 (m, 4H), 7.77 (s, 1H).	108.6
化合物 54		δ 2.75 (d, J = 2.0Hz, 1H), 5.86 (d, J = 2.0Hz, 1H), 7.17-7.71 (m, 11H), 7.78 (s, 1H).	92.9
化合物 55		δ 0.94 (t, J = 7.2Hz, 6H), 1.26-1.54 (m, 4H), 1.57-1.73 (m, 4H), 4.27 (quint, J = 5.9Hz, 1H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.26 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	84.7
化合物 56		δ 2.09-2.15 (m, 2H), 2.14 (s, 3H), 2.71 (t, J = 7.0Hz, 2H), 4.11 (t, J = 6.1Hz, 2H), 6.99 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.30 (m, J_{AB} = 8.8Hz, 2H), 7.78 (s, 1H).	95.0

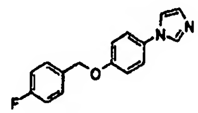
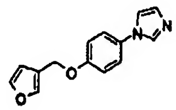
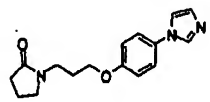
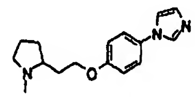
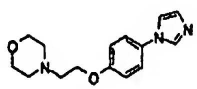
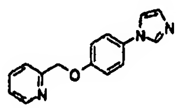
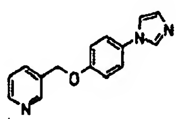
[0056]
[Table 9]

化合物 57		δ 2.29 (quint, J = 6.0Hz, 2H), 4.18 (t, J = 6.1Hz, 2H), 4.21 (t, J = 6.1Hz, 2H), 6.91-7.02 (m, 5H), 7.18 (s, 1H), 7.20 (s, 1H), 7.26-7.33 (m, 4H), 7.76 (s, 1H).	98.0
化合物 58		δ 1.61 (s, 3H), 1.76 (s, 3H), 1.82 (s, 3H), 2.08-2.17 (m, 4H), 4.58 (d, J = 6.7Hz, 2H), 5.09 (m, 1H), 5.49 (t, J = 6.7Hz, 1H), 6.99 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.77 (s, 1H).	100.7
化合物 59		δ 1.13-1.82 (m, 9H), 2.26-2.62 (m, 2H), 3.85-4.00 & 3.28-3.69 (m, 2H), 6.99 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	96.1
化合物 60		δ 0.87-0.94 (m, 2H), 1.08-1.33 (m, 6H), 1.43-1.53 (m, 2H), 1.63-1.83 (m, 7H), 3.98 (t, J = 6.5 Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	58.8
化合物 61		δ 0.74 (s, 3H), 1.21 (s, 3H), 2.15 (dt, J = 5.1, 6.5Hz, 2H), 3.46 (d, J = 11.0Hz, 2H), 3.63 (d, J = 11.0Hz, 2H), 4.14 (t, J = 6.5Hz, 2H), 4.70 (t, J = 5.1Hz, 1H), 6.99 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	91.8
化合物 62		δ 1.26 (t, J = 7.1Hz, 3H), 1.45-1.58 (m, 2H), 1.65-1.75 (m, 2H), 1.77-1.88 (m, 2H), 2.35 (t, J = 7.4Hz, 2H), 3.99 (t, J = 6.4Hz, 2H), 4.14 (q, J = 7.1Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	98.0
化合物 63		δ 3.09 (t, J = 6.8Hz, 2H), 4.20 (t, J = 6.8Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.17-7.32 (m, 5H), 7.39 (ddd, J = 1.7, 2.1, 7.1Hz, 1H), 7.45 (d, J = 1.7Hz, 1H), 7.76 (s, 1H).	92.9

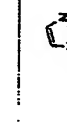
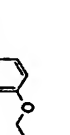
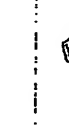
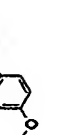
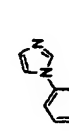
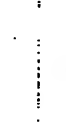
[0057]
[Table 10]

化合物 64		δ 3.23 (t, J = 6.7Hz, 2H), 4.21 (t, J = 6.7Hz, 2H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.23-7.30 (m, 4H), 7.41 (d, J = 2.2Hz, 1H), 7.78 (s, 1H).	83.2
化合物 65		δ 5.14 (s, 2H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.20 (s, 1H), 7.22 (s, 1H), 7.33 (m, J_{AB} = 8.9Hz, 2H), 7.50-7.56 (m, 1H), 7.64-7.70 (m, 2H), 7.77 (s, 1H).	76.9
化合物 66		δ 1.21 (t, J = 7.2Hz, 3H), 2.32 (s, 3H), 3.48 (q J = 7.2Hz, 2H), 3.74 (t, J = 6.2Hz, 2H), 4.15 (t, J = 6.2Hz, 2H), 6.53-6.67 (m, 3H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.10-7.16 (m, 1H), 7.20 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.80 (s, 1H).	85.1
化合物 67		δ 1.63-1.82 (m, 6H), 2.40 & 2.43 (m, 3H), 2.60-2.91 (m, 3H), 4.05 & 4.52 (m, 1H), 6.96 (m, 8.0Hz, 2H), 7.19 (d, J = 5.6Hz, 2H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	40.2
化合物 68		δ 2.24 (tt, J = 5.9, 6.7Hz, 2H), 3.91 (t, J = 5.9Hz, 2H), 4.14 (t, J = 6.7Hz, 2H), 6.15 (dd, J = 2.0, 2.2Hz, 2H), 6.66 (dd, J = 2.0, 2.2Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.20 (s, 1H), 7.21 (s, 1H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.78 (s, 1H).	110.5
化合物 69		δ 1.88 (t, J = 2.2Hz, 3H), 4.70 (q, J = 2.2Hz, 2H), 7.06 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.22 (s, 1H), 7.32 (m, J_{AB} = 8.8Hz, 2H), 7.78 (s, 1H). mp 81.0-83.5℃	80.6 7.2
化合物 70		δ 0.99 (t, J = 7.3Hz, 3H), 1.49 (sext, J = 7.3Hz, 2H), 1.73-1.87 (m, 2H), 4.00 (t, J = 6.4Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H). mp 47.0-50.0℃	98.3

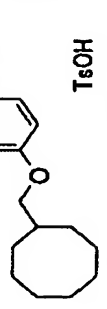
[0058]
[Table 11]

化合物 71		δ 5.07 (s, 2H), 7.03-7.46 (m, 10H), 7.77 (s, 1H). mp 91.5-93.0°C	109.0	1.3
化合物 72		δ 4.99 (s, 2H), 6.51 (d, J = 1.1Hz, 1H), 7.01-7.09 (m, 2H), 7.19-7.36 (m, 4H), 7.46 (t, J = 1.7Hz, 1H), 7.54 (dd, J = 0.9, 1.7Hz, 1H), 7.78 (t, J = 1.1Hz, 1H). mp 114.5-115.5°C	99.3	4.7
化合物 73		δ 2.01-2.13 (m, 4H), 2.40 (t, J = 8.4Hz, 2H), 3.38-3.54 (m, 4H), 4.03 (t, J = 6.2Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	72.4	7.3
化合物 74		δ 2.58-2.67 (m, 4H), 2.84 (t, J = 5.7Hz, 2H), 3.71-3.78 (m, 4H), 4.15 (t, J = 5.7Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	55.2	33.5
化合物 75		δ 2.60 (m, 4H), 2.83 (t, J = 5.6Hz, 2H), 3.75 (m, 4H), 4.15 (t, J = 5.6Hz, 2H), 7.00 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H). mp 41.0-43.5°C	66.7	8.6
化合物 76		(200 MHz, *DMSO-d_6*) δ 5.24 (s, 2H), 7.08 (t, J = 1.1Hz, 2H), 7.10-7.21 (m, 2H), 7.37 (m, 1H), 7.50-7.63 (m, 3H), 7.65 (t, J = 1.3Hz, 1H), 7.78 (dt, J = 1.8, 7.7Hz, 1H), 8.14 (t, J = 1.1Hz, 1H), 8.60 (m, 1H). mp 94.0-95.0°C	70.8	4.5
化合物 77		δ 5.14 (s, 2H), 7.07 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.27-7.79 (m, 3H), 7.78-7.83 (m, 2H), 8.63 (dd, J = 1.8, 4.8Hz, 1H), 8.72 (d, J = 2.2Hz, 1H). mp 117.5-119.0°C	93.7	0.63

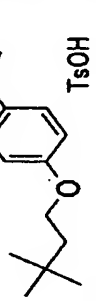
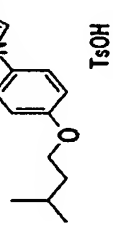
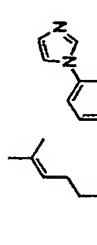
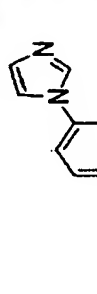
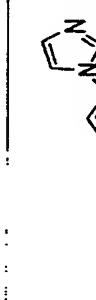
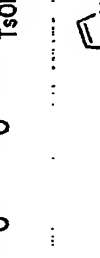
[0059]
[Table 12]

化合物 78		(200 MHz, *DMSO-d_6*) δ 5.26 (s, 2H), 7.09-7.23 (m, 3H), 7.43-7.70 (m, 5H), 8.20 (s, 1H), 8.60 (dd, J = 1.8, 4.6Hz, 2H). mp 104.0-106.0℃	95.1	4.9
化合物 79		δ 1.05 (t, J = 7.2Hz, 6H), 2.62 (q, J = 7.2Hz, 4H), 2.73 (t, J = 6.2Hz, 2H), 3.67 (t, J = 6.2Hz, 2H), 3.84 (m, 2H), 4.16 (m, 2H), 7.01 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	34.8	62.6
化合物 80		δ 2.16 (ddt, J = 6.2, 7.3, 8.1Hz, 2H), 2.85 (dd, J = 7.3, 8.1Hz, 2H), 4.00 (t, J = 6.2Hz, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.15-7.22 (m, 4H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.77 (s, 1H), 8.51-8.54 (m, 2H). mp 70.0-72.0℃	94.7	1.1
化合物 81		δ 2.28 (ddt, J = 6.2, 7.0, 8.1Hz, 2H), 3.01 (dd, J = 7.0, 8.1Hz, 2H), 4.05 (t, J = 6.2Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.11-7.21 (m, 4H), 7.30 (m, J_{AB} = 9.0Hz, 2H), 7.61 (dt, J = 1.8, 7.5Hz, 1H), 7.76 (s, 1H), 8.56 (d, J = 4.0Hz, 1H). mp 64.0-66.0℃	79.0	2.1
化合物 82		δ 1.01 (s, 6H), 2.29 (s, 6H), 2.30 (s, 2H), 3.74 (s, 2H), 7.01 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.78 (s, 1H). mp 64.0-66.0℃	55.8	108.3
化合物 83		(200 MHz, *DMSO-d_6*) δ 4.27 (s, 4H), 6.00 (t, J = 2.2Hz, 2H), 6.85 (t, J = 2.2Hz, 2H), 7.00-7.13 (m, 3H), 7.49-7.60 (m, 2H), 7.64 (t, J = 1.3Hz, 1H), 8.13 (t, J = 1.1Hz, 1H). mp 128.5-129.0℃	110.5	0.8
化合物 84	 TsOH	*DMSO-d_6*, δ 0.36 (m, 2H), 0.60 (m, 2H), 1.25 (m, 1H), 2.29 (s, 3H), 3.91 (d, J = 7.0Hz, 2H), 7.10-7.21 (m, 4H), 7.49 (m, J_{AB} = 7.9Hz, 2H), 7.71 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.22 (dd, J = 1.5, 1.9Hz, 1H), 9.60 (dd, J = 1.3, 1.5Hz, 1H). mp 136.0-138.0℃	71.8	12.5

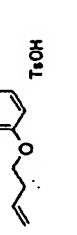
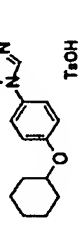
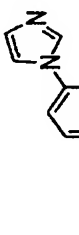
[0060]
[Table 13]

化合物 85		(200 MHz, *DMSO-d_6*), δ 1.28-2.15 (m, 15H), 2.29 (s, 3H), 3.84 (d, J = 6.6Hz, 2H), 7.08-7.25 (m, 4H), 7.48 (m, J_{AB} =8.1Hz, 2H), 7.70 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.5, 1.8Hz, 1H), 8.21 (dd, J = 1.3, 1.8Hz, 1H), 9.56 (dd, J = 1.3, 1.5Hz, 1H). mp 232.5-233.0℃	91.6	2.7
化合物 86		(200 MHz, *DMSO-d_6*) δ 1.10 (s, 3H), 1.13 (s, 3H), 2.29 (s, 3H), 3.55-3.78 (m, 3H), 4.13-4.20 (m, 2H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.2Hz, 2H), 7.48 (m, J_{AB} =8.1Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.5, 1.8Hz, 1H), 8.22 (dd, J = 1.3, 1.8Hz, 1H), 9.58 (dd, J = 1.3, 1.5Hz, 1H). mp 150.0-153.0℃	90.0	5.5
化合物 87		*DMSO-d_6*, δ 2.29 (s, 3H), 3.25 (s, 3H), 3.48 (m, 2H), 3.60 (m, 2H), 3.76 (m, 2H), 4.20 (m, 2H), 7.11 (m, J_{AB} = 8.1Hz, 2H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.23 (dd, J = 1.5, 1.9Hz, 1H), 9.61 (dd, J = 1.3, 1.5Hz, 1H). mp 113.0-116.0℃	72.1	32.4
化合物 88		(200 MHz, *DMSO-d_6*) δ 1.10 (t, J = 7.0Hz, 3H), 2.29 (s, 3H), 3.38-3.65 (m, 6H), 3.74-3.83 (m, 2H), 4.15-4.25 (m, 2H), 7.12 (m, J_{AB} = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, J = 1.3, 1.8Hz, 1H), 8.22 (dd, J = 1.5, 1.8Hz, 1H), 9.59 (dd, J = 1.3, 1.5Hz, 1H). mp 117.0-117.5℃	68.4	18.5
化合物 89		(200 MHz, *DMSO-d_6*) δ 0.88 (t, J = 7.0Hz, 3H), 1.23-1.60 (m, 4H), 2.29 (s, 3H), 3.46 (t, J = 6.4Hz, 2H), 3.69-3.75 (m, 2H), 4.13-4.23 (m, 2H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.5, 1.8Hz, 1H), 8.22 (dd, J = 1.3, 1.8Hz, 1H), 9.59 (dd, J = 1.3, 1.5Hz, 1H). mp 137.0-139.0℃	96.7	4.1
化合物 90		*DMSO-d_6*, δ 2.17 (s, 1H), 2.29 (s, 3H), 2.88 (t, J = 6.6Hz, 1H), 4.24 (t, J = 6.6Hz, 2H), 7.12 (m, J_{AB} = 8.0Hz, 2H), 7.20 (m, J_{AB} = 9.2Hz, 2H), 7.49 (m, J_{AB} = 8.0Hz, 2H), 7.73 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.23 (dd, J = 1.5, 1.9Hz, 1H), 9.61 (dd, J = 1.3, 1.5Hz, 1H). mp 140.0-142.0℃	91.8	7.5

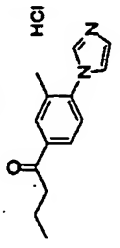
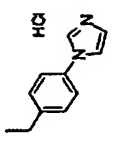
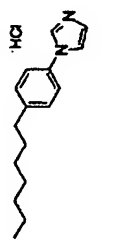
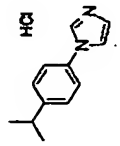
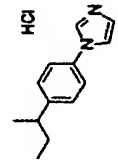
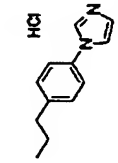
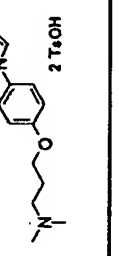
[0061]
[Table 14]

化合物 91		(200 MHz, *DMSO-d_6*) δ 0.98 (s, 9H), 1.68 (t, J = 7.0Hz, 2H), 2.29 (s, 3H), 4.11 (t, J = 7.0Hz, 2H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.5, 1.8Hz, 1H), 8.21 (dd, J = 1.3, 1.8Hz, 1H), 9.58 (dd, J = 1.3, 1.5Hz, 1H). mp 220.0-221.0℃	101.8	1.8
化合物 92		*DMSO-d_6*, δ 0.95 (d, J = 6.4Hz, 6H), 1.64 (q, J = 6.4Hz, 2H), 1.80 (m, 1H), 2.29 (s, 3H), 4.08 (t, J = 6.4Hz, 2H), 7.12 (m, J_{AB} = 7.9Hz, 2H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} =7.9Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.21 (dd, J = 1.5, 1.9Hz, 1H), 9.59 (dd, J = 1.3, 1.5Hz, 1H). mp 187.0-189.0℃	102.8	2.3
化合物 93		(200 MHz, *DMSO-d_6*) δ 0.93 (d, J = 6.2Hz, 3H), 1.08-2.10 (m, 13H), 2.29 (s, 3H), 4.09 (t, J = 7.0Hz, 2H), 5.10 (m, 1H), 7.08-7.25 (m, 4H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.3, 2.0Hz, 1H), 8.21 (dd, J = 1.5, 2.0Hz, 1H), 9.58 (dd, J = 1.3, 1.5Hz, 1H). mp 152.0-153.0℃	100.2	5.3
化合物 94		*DMSO-d_6*, δ 0.99 (t, J = 7.5Hz, 3H), 1.76 (tq, J = 6.6, 7.5Hz, 2H), 2.29 (s, 3H), 4.02 (t, J = 6.6Hz, 2H), 7.12 (m, J_{AB} = 7.9Hz, 2H), 7.17 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} =7.9Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.22 (dd, J = 1.5, 1.9Hz, 1H), 9.61 (dd, J = 1.3, 1.5Hz, 1H). mp 148.0-150.0℃	82.7	7.7
化合物 95		(200 MHz, *DMSO-d_6*) δ 1.11 (t, J = 7.0Hz, 3H), 1.90-2.05 (m, 2H), 2.29 (s, 3H), 3.44 (q, J = 7.0Hz, 2H), 3.52 (t, J = 6.2Hz, 2H), 4.11 (t, J = 6.4Hz, 2H), 7.11 (m, J_{AB} = 8.3Hz, 2H), 7.19 (m, J_{AB} = 9.2Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.5, 1.8Hz, 1H), 8.21 (dd, J = 1.3, 1.8Hz, 1H), 9.58 (dd, J = 1.3, 1.5Hz, 1H). mp 122.5-124.0℃	94.3	2.0
化合物 96		*DMSO-d_6*, δ 1.77 (t, J = 2.6Hz, 3H), 2.29 (s, 3H), 2.58-2.66 (m, 2H), 4.12 (t, J = 6.7Hz, 2H), 7.11 (d, J= 7.7Hz, 2H), 7.20 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB}= 9.0Hz, 2H), 7.89 (t, J = 1.5, 1.8Hz, 1H), 8.22 (t, J = 1.3, 1.8Hz, 1H), 9.58 (t, J = 1.3, 1.5Hz, 1H). mp 147.5-149.5℃	95.8	5.0

[0062]
[Table 15]

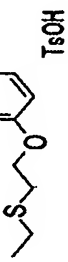
化合物 97		(200 MHz, *DMSO-d_6*) δ 2.29 (s, 3H), 2.45-2.58 (m, 2H), 4.12 (t, J = 6.6Hz, 2H), 5.05-5.25 (m, 2H), 5.90 (m, 1H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.5, 1.8Hz, 1H), 8.21 (dd, J = 1.3, 1.8Hz, 1H), 9.58 (dd, J = 1.3, 1.5Hz, 1H). mp 133.5-134.5℃	101.9	2.5
化合物 98		(200 MHz, *DMSO-d_6*) δ 1.13-2.05 (m, 10H), 2.29 (s, 3H), 4.47(m, 1H), 7.11 (m, J_{AB} = 7.7Hz, 2H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.68 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.5, 1.8Hz, 1H), 8.20 (dd, J = 1.3, 1.8Hz, 1H), 9.56 (dd, J = 1.3, 1.5Hz, 1H). mp 187.5-188.0℃	98.2	3.7
化合物 99		*DMSO-d_6*, δ 0.99 (d, J = 6.6Hz, 6H), 2.05 (m, 1H), 2.29 (s, 3H), 3.84 (d, J = 6.6Hz, 2H), 7.11 (d, J_{AB}= 8.1Hz, 2H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB}= 9.0Hz, 2H), 7.88 (t, J = 1.5, 1.8Hz, 1H), 8.20 (t, J = 1.3, 1.8Hz, 1H), 9.55 (t, J = 1.3, 1.5Hz, 1H). mp 176.5-178.0℃	100.6	4.3
化合物 100		(200 MHz, *DMSO-d_6*) δ 2.05-2.23 (m, 2H), 2.99 (t, J =7.9Hz, 2H), 4.11 (t, J = 6.4Hz, 2H), 7.16 (m, J_{AB} = 9.2Hz, 2H), 7.74 (m, J_{AB} = 9.2Hz, 2H), 7.88-8.03 (m, 2H), 8.23 (dd, J = 1.3, 1.8Hz, 1H), 8.48 (m, 1H), 8.77 (dd, J = 0.9 5.5Hz, 1H), 8.86 (d, J = 2.0Hz, 1H), 9.69 (dd, J = 1.3, 1.5Hz, 1H). mp 252.0-253.0℃	99.1	1.1
化合物 101		(200 MHz, *DMSO-d_6*) δ 1.28-1.85 (m, 8H), 2.69 (s, 3H), 2.72 (s, 3H), 2.91-3.10 (m, 2H), 4.07 (t, J = 6.4Hz, 2H), 7.18 (m, J_{AB} = 9.2Hz, 2H), 7.73 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.5, 1.8Hz, 1H), 8.22 (dd, J = 1.3, 1.8Hz, 1H), 9.65 (dd, J = 1.3, 1.5Hz, 1H). mp 205.0-207.0℃	90.0	2.2
化合物 102		δ 0.96 (t, J = 7.3 Hz, 3H), 1.35-1.42 (m, 2H), 1.58-1.68 (m, 2H), 2.18 (s, 3H), 2.67 (t, J = 7.6 Hz, 2H), 7.21-7.28 (m, 4H), 7.62 (dd, J = 1.4, 1.7Hz, 1H), 8.74 (dd, J = 1.2, 1.4Hz, 1H). mp 152.0-153.0℃		

[0063]
[Table 16]

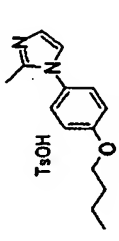
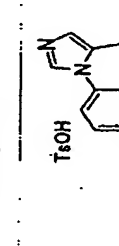
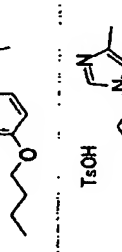
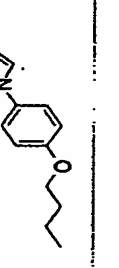
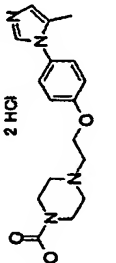
化合物 103		δ 1.03 (t, J = 7.5 Hz, 3H), 1.76-1.83 (m, 2H), 2.34 (s, 3H), 2.98 (t, J = 7.3 Hz, 2H), 7.29 (dd, J = 1.3, 1.6Hz, 1H), 7.53 (d, J = 8.2Hz, 1H), 7.66 (dd, J = 1.5, 1.6Hz, 1H), 7.97 (dd, J = 1.9, 8.2Hz, 1H), 8.00 (d, J = 1.9Hz, 1H), 9.35 (dd, J = 1.3, 1.5Hz, 1H). mp 199.5-201.0℃
化合物 104		(200 MHz) δ 1.30 (t, J = 7.5 Hz, 3H), 2.76 (q, J = 7.5 Hz, 2H), 7.40-7.50 (m, 5H), 7.58 (d, J = 1.3Hz, 1H), 9.05 (s, 1H).
化合物 105		(200 MHz) δ 0.89 (t, J = 6.8 Hz, 3H), 1.13-1.43 (m, 8H), 1.50-1.75 (m, 2H), 2.70 (t, J = 7.3 Hz, 2H), 7.35-7.65 (m, 6H), 9.35 (dd, J = 1.3, 1.5Hz, 1H).
化合物 106		(200 MHz) δ 1.28 (s, 3H), 1.31 (s, 3H), 3.02 (m, 1H), 7.40-7.63 (m, 6H), 9.43 (dd, J = 1.3, 1.5Hz, 1H). mp 205.5-207.5℃
化合物 107		(200 MHz) δ 0.85 (t, J = 7.5 Hz, 3H), 1.28 (d, J = 6.8Hz, 3H), 1.55-1.75 (m, 2H), 2.63-2.84 (m, 2H), 7.38-7.53 (m, 5H), 7.59 (dd, J = 1.3, 1.8Hz, 1H), 9.13 (dd, J = 1.3, 1.5Hz, 1H). mp 142.0-146.0℃
化合物 108		(200 MHz) δ 0.97 (t, J = 7.3Hz, 3H), 1.58-1.80 (m, 2H), 2.69 (t, J = 7.3Hz, 2H), 7.35-7.55 (m, 5H), 7.59 (dd, J = 1.3, 1.8Hz, 1H), 9.29 (dd, J = 1.3, 1.5Hz, 1H). mp 155.5-157.0℃
化合物 109		*DMSO-d_6*, δ 2.29 (s, 6H), 2.29 (s, 6H), 2.83 (s, 3H), 2.85 (s, 3H), 3.24 (m, 2H), 4.13 (t, J = 6.0Hz, 2H), 7.12 (m, J_{AB} = 8.0Hz, 4H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} = 8.0Hz, 4H), 7.74 (m, J_{AB} = 9.0Hz, 2H), 7.92 (dd, J = 1.3, 1.9Hz, 1H), 8.22 (dd, J = 1.5, 1.9Hz, 1H), 9.61 (dd, J = 1.3, 1.5Hz, 1H). mp 95.0-98.0℃

35.9 50.6

[0064]
[Table 17]

化合物 110	 TsOH	*DMSO-d_6*, δ 1.21 (t, *J* = 7.5Hz, 3H), 2.29 (s, 3H), 2.64 (q, *J* = 7.5Hz, 2H), 2.91 (t, *J* = 6.6Hz, 2H), 4.23 (t, *J* = 6.6Hz, 2H), 7.11 (d, *J* = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.2Hz, 2H), 7.49 (d, *J* = 7.9Hz, 2H), 7.73 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, *J* = 1.3, 1.9Hz, 1H), 8.22 (dd, *J* = 1.5, 1.9Hz, 1H), 9.61 (dd, *J* = 1.3, 1.5Hz, 1H). mp 147.0–149.0℃	97.9	1.8
化合物 111		*DMSO-d_6*, δ 1.28 (t, *J* = 7.3Hz, 6H), 3.10–3.30 (m, 4H), 3.46–3.58 (m, 2H), 4.51 (t, *J* = 5.0Hz, 2H), 7.25 (m, J_{AB} = 9.0Hz, 2H), 7.78 (m, J_{AB} = 8.9Hz, 2H), 7.90 (dd, *J* = 1.5, 1.8Hz, 1H), 8.23 (dd, *J* = 1.3, 1.8Hz, 1H), 9.66 (dd, *J* = 1.3, 1.5Hz, 1H). mp 228.0–230.0℃	33.0	49.5
化合物 112		*DMSO-d_6*, δ 2.73 (s, 3H), 5.52 (s, 2H), 7.32 (m, J_{AB} = 9.2Hz, 2H), 7.68 (d, *J* = 7.9Hz, 1H), 7.73–7.83 (m, 3H), 7.92 (dd, *J* = 1.5, 1.8Hz, 1H), 8.20–8.30 (m, 2H), 9.72 (dd, *J* = 1.3, 1.5Hz, 1H). mp 236.0–237.0℃	80.4	17.6
化合物 113		*DMSO-d_6*, δ 1.26 (m, 1H), 1.88 (m, 2H), 2.73 (s, 1H), 2.73–2.87 (m, 2H), 3.26–3.51 (m, 2H), 3.93 (dd, *J* = 7.3, 9.6Hz, 1H), 4.05 (dd, *J* = 4.7, 9.6Hz, 1H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.75 (m, J_{AB} = 9.0Hz, 2H), 7.90 (d, *J* = 1.4Hz, 1H), 8.23 (d, *J* = 1.4Hz, 1H), 9.65 (d, *J* = 1.4Hz, 1H). mp 232.0–242.0℃	82.2	6.8
化合物 114		δ 3.09 (t, *J* = 4.5Hz, 4H), 3.90 (t, *J* = 4.5Hz, 4H), 7.12 (d, *J* = 8.7Hz, 1H), 7.20 (s, 1H), 7.22 (s, 1H), 7.27 (dd, *J* = 2.5, 8.7Hz, 1H), 7.45 (d, *J* = 2.5Hz, 1H), 7.79 (s, 1H). mp 127.0–129.0℃		40.8
化合物 115	2 TsOH	*DMSO-d_6*, δ 2.29 (s, 6H), 2.89 brs, 6H), 3.57 (m, 2H), 4.41 (brt, *J* = 5.3Hz, 2H), 7.12 (brd, *J* = 7.9Hz, 4H), 7.25 (m, J_{AB} = 9.0Hz, 2H), 7.49 (brd, *J* = 7.9Hz, 4H), 7.77 (m, J_{AB} = 9.0Hz, 2H), 7.93 (t, *J* = 1.5Hz, 1H), 8.24 (t, *J* = 1.5Hz, 1H), 9.63 (d, *J* = 1.5Hz, 1H). mp 161.0–164.0℃	19.4	387.4
化合物 116	2 HCl	*DMSO-d_6*, δ 2.76 (s, 3H), 2.77 (s, 3H), 3.27 (m, 2H), 3.80–3.91 (m, 4H), 4.25 (m, 2H), 7.21 (m, J_{AB} = 9.0Hz, 2H), 7.76 (m, J_{AB} = 9.0Hz, 2H), 7.91 (dd, *J* = 1.3, 1.9Hz, 1H), 8.24 (dd, *J* = 1.5, 1.9Hz, 1H), 9.71 (dd, *J* = 1.3, 1.5Hz, 1H). mp 174.0–179.0℃	57.2	9.0

[0065]
[Table 18]

化合物 117		*DMSO-d_6*, δ 1.00 (t, J = 7.3Hz, 3H), 1.52 (m, 2H), 1.83 (m, 2H), 2.37 (s, 3H), 2.68 (s, 3H), 4.04 (t, J = 6.4Hz, 2H), 7.18-7.27 (m, 4H), 7.42 (s, 1H), 7.88 (m, J_{AB} = 8.1Hz, 2H). mp 148.0-149.0℃	>300.0
化合物 118		*DMSO-d_6*, δ 0.95 (t, J = 7.3Hz, 3H), 1.45 (tq, J = 7.3, 7.7Hz, 2H), 1.67-1.80 (m, 2H), 2.17 (d, J = 0.9Hz, 3H), 2.29 (s, 3H), 4.07 (t, J = 6.5Hz, 2H), 7.09-7.21 (m, 4H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.55 (m, J_{AB} = 8.8Hz, 2H), 9.25 (d, J = 1.5Hz, 1H). mp 163.0-164.0℃	3.4
化合物 119		δ 0.99 (t, J = 7.3Hz, 3H), 1.45 (tq, J = 7.3, 7.7Hz, 2H), 1.72-1.83 (m, 2H), 2.17 (d, J = 0.9Hz, 3H), 3.99 (t, J = 6.5Hz, 2H), 6.92-7.00 (m, 1H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.26 (m, J_{AB} = 9.0Hz, 2H), 7.66 s, 1H). mp 130.0-130.5℃	173.1
化合物 120		*DMSO-d_6*, δ 1.21 (t, J = 7.0Hz, 3H), 2.17 (s, 3H), 3.11-3.50 (m, 8H), 3.55 (t, J = 4.8Hz, 2H), 4.09 (q, J = 7.0Hz, 2H), 4.52 (t, J = 4.8Hz, 2H), 7.25 (m, J_{AB} = 9.0Hz, 2H), 7.56-7.84 (m, 3H), 9.26 (s, 1H). mp 212.0-214.5℃	56.5
化合物 121		*DMSO-d_6*, δ 1.21 (t, J = 7.2Hz, 3H), 3.00-3.83 (m, 8H), 3.56 (t, J = 4.8Hz, 2H), 4.09 (q, J = 7.2Hz, 2H), 4.54 (t, J = 4.7Hz, 2H), 7.26 (m, J_{AB} = 9.0Hz, 2H), 7.78 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.4, 1.9Hz, 1H), 8.21 (dd, J = 1.4, 1.9Hz, 1H), 9.64 (t, J = 1.4Hz, 1H). mp 199.5-202.0℃	16.2

[0066]
The example of a trial [inhibitory action of a Homo sapiens kidney microsome origin 20-HETE production enzyme]

20-HETE production inhibitory action was examined about the compound given [above-mentioned] in a table.
The exam was performed based on J.Pharmacol.Exp.Ther., the 268th volume, and the approach of a page [474th] (1994) publication.
3-morpholino propane sulfonic acid of 50mM(s) which contain the magnesium chloride of 5mM, and ethylenediamine tetra-acetic acid JISODIUMUSORUTO (EDTA) of 1mM for the test drug solution prepared to 1microM by DMSO (MOPS) (pH7.4) It adds to the buffer solution. As a source of an enzyme, a Homo sapiens kidney microsome fraction (Human Cell Culture Center, Anatomic Gift Foundation), The [5, 6, 8, 9, 11, 12, 14, 15] tritium-arachidonic acid was added as a substrate, NADPH was added as a coenzyme, and it was made to react at 37 degrees for 1.5 hours. After adding the formic acid to reaction mixture and making it suspend a reaction, the acetonitrile (50% of final concentration) was added. The amount of production of 20-HETE was measured using the high performance chromatography with a radioactive substance detector equipped with an ODS column (the biotechnology sill C18, Bio-Rad make).
[0067]
The amount of production of 20-HETE at the time of compound additive-free was made into 100%, and the rate of control (%) was computed from the amount of 20-HETE production when adding a compound. The result is collectively shown in the above-mentioned table 1.
Moreover, the amount of production of 20-HETE at the time of compound additive-free was made into 100%, and the 20-HETE production when adding a compound also computed the compound concentration (IC50 value) checked 50%. The result is also collectively shown in the above-mentioned table 1.

[Translation done.]

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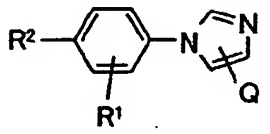
最終頁に続く

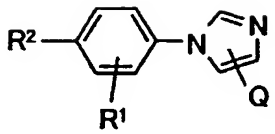
(54)【発明の名称】イミダゾール誘導体

(57)【要約】
【課題】腎臓、脳血管等の主要臓器における微小血管収縮、拡張作用、細胞増殖惹起作用等に関与している２０－ＨＥＴＥの産生酵素を阻害する薬剤を提供すること。
【解決手段】式
【化１０】

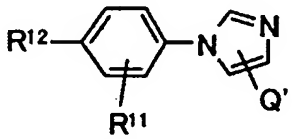


{式中、Ｑは水素原子またはC_1～C_4アルキル基であり、R^1は、水素原子、C_1～C_6アルキル基、ハロゲン原子であり、R^2はC_1～C_{14}アルキル基、C_2～C_{14}アルカノイル基、モルホリノ基又は式R^3－Ｏ－［式中、R^3は、C_1～C_{14}アルキル基、C_2～C_{14}アルケニル基、C_3～C_{14}アルキニル基、C_3～C_{10}シクロアルキル基、１－フェニル－２－プロピニル基又は式R^4－Ａ－で示される基である。］で示される基である。}で表されるイミダゾール誘導体又はその製薬学的に許容される塩を有効成分として含むことを特徴とする２０－ＨＥＴＥ産生酵素阻害剤。
【選択図】　なし

【特許請求の範囲】
【請求項１】
式
【化１】



｛式中、Ｑは水素原子またはＣ１～Ｃ４アルキル基であり、Ｒ１は、水素原子、Ｃ１～Ｃ６アルキル基、ハロゲン原子であり、Ｒ２はＣ１～Ｃ１４アルキル基、Ｃ２～Ｃ１４アルカノイル基、モルホリノ基又は式Ｒ３－Ｏ－［式中、Ｒ３はＣ１～Ｃ１４アルキル基、Ｃ２～Ｃ１４アルケニル基、Ｃ３～Ｃ１４アルキニル基、Ｃ３～Ｃ１０シクロアルキル基、１－フェニル－２－プロピニル基又は式Ｒ４－Ａ－（式中、Ｒ４はＣ３～Ｃ１０シクロアルキル基、Ｃ１～Ｃ１０アルコキシ基、Ｃ２～Ｃ１０アルカノイル基、Ｃ２～Ｃ６アルコキシカルボニル基、ジオキソラニル基、Ｃ１～Ｃ６アルキル基で置換されたジオキソラニル基、オキサニル基、ジオキサニル基、Ｃ１～Ｃ６アルキル基で置換されたジオキサニル基、ベンゾジオキサニル基、ビシクロ［２．２．１］ヘプタン－２－イル基、Ｃ１～Ｃ６アルキルチオ基、ピロリジニル基、Ｃ１～Ｃ６アルキル基で置換されたピロリジニル基、ピペリジニル基、Ｃ１～Ｃ６アルキル基で置換されたピペリジニル基、モルホリノ基、４－Ｃ２～Ｃ６アルコキシカルボニルピペラジン－１－イル基、ピロリル基、ピリジル基、Ｎ，Ｎ－ジＣ１～Ｃ６アルキルアミノ基、Ｎ，Ｎ－ジＣ１～Ｃ６アルキルアミノＣ１～Ｃ６アルコキシ基、Ｃ１～Ｃ６アルコキシＣ１～Ｃ６アルコキシ基、フェノキシ基、フェニル基、「Ｃ１～Ｃ６アルキル基、Ｃ１～Ｃ６アルコキシ基、ハロゲン原子、フェニルエチル基、フェノキシ基、ニトリル及びメチルチオ基」から選ばれる基の１又は２個で置換されたフェニル基、ビフェニル基、フェニルチオ基、フリル基、チエニル基、チアゾリル基、Ｃ１～Ｃ６アルキル基で置換されたチアゾリル基、トルイジノ基、Ｎ－Ｃ１～Ｃ６アルキルトルイジノ基、ピロリドン－１－イル基であり、ＡはＣ１～Ｃ１０アルキレン基である。）で示される基である。］で示される基である。｝で表されるイミダゾール誘導体又はその製薬学的に許容される塩を有効成分として含むことを特徴とする２０－ＨＥＴＥ産生酵素阻害剤。
【請求項２】
式
【化２】



｛式中、Ｑ’は水素原子またはＣ１～Ｃ４アルキル基であり、Ｒ１１は、水素原子、Ｃ１～Ｃ６アルキル基、ハロゲン原子であり、Ｒ１２はモルホリノ基又は式Ｒ１３－Ｏ－［式中、Ｒ１３は、Ｃ３～Ｃ１４アルキニル基、Ｃ３～Ｃ１０シクロアルキル基、１－フェニル－２－プロピニル基又は式Ｒ１４－Ａ’－（式中、Ｒ１４はＣ３～Ｃ１０シクロアルキル基、Ｃ１～Ｃ１０アルコキシ基、Ｃ２～Ｃ１０アルカノイル基、ジオキソラニル基、Ｃ１～Ｃ６アルキル基で置換されたジオキソラニル基、オキサニル基、ジオキサニル基、Ｃ１～Ｃ６アルキル基で置換されたジオキサニル基、ベンゾジオキサニル基、ビシクロ［２．２．１］ヘプタン－２－イル基、Ｃ１～Ｃ６アルキルチオ基、４－Ｃ２～Ｃ６アルコキシカルボニルピペラジン－１－イル基、ピロリル基、Ｎ，Ｎ－ジＣ１～Ｃ６アルキルアミノＣ１～Ｃ６アルコキシ基、Ｃ１～Ｃ６アルコキシＣ１～Ｃ６アルコキシ基、フリル基、チエニル基、ピロリドン－１－イル基であり、Ａ’はＣ１～Ｃ１０アルキレン基である。

）で示される基である。］で示される基である。｝で表されるイミダゾール誘導体又はその製薬学的に許容される塩。
【請求項３】
請求項２記載のイミダゾール誘導体又はその製薬学的に許容される塩を有効成分とする医薬。
【請求項４】
２０－ＨＥＴＥ産生酵素阻害剤である請求項３記載の医薬。
【請求項５】
腎疾患、脳血管疾患又は循環器疾患治療薬である請求項３記載の医薬。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】
本発明は、アラキドン酸から生合成される２０－ヒドロキシエイコサテトラエン酸（２０－ＨＥＴＥ）の産生酵素を阻害するイミダゾール誘導体に関する。
【０００２】
【従来の技術】
アラキドン酸から産生される生理活性物質として、シクロオキシゲナーゼによって産生されるプロスタグランジン類及びリポキシゲナーゲによって産生されるロイコトリエン類が広く知られている。しかし、近年、チトクロームｐ４５０属に属する酵素によってアラキドン酸から産生される２０－ＨＥＴＥが生体内で多彩な働きをしていることが明らかとされつつある。これまでに２０－ＨＥＴＥは腎臓、脳血管等の主要臓器において微小血管を収縮又は拡張させることや細胞増殖を惹起することが明らかにされており、生体内で重要な生理作用を演じていると共に各種腎疾患、脳血管疾患、循環器疾患等の病態に深く関与していることが示唆されている（Ｊ．　Ｖａｓｃｕｌａｒ　Ｒｅｓｅａｒｃｈ，第３２巻，第７９頁，　１９９５年、Ａｍ．　Ｊ．　Ｐｈｙｓｉｏｌ．，第２７７巻，　Ｒ６０７頁，１９９９年、Ｐｈｙｓｉｏｌ．　Ｒｅｖ．，第８２巻，第１３１項，２００２年）。
【０００３】
また、本発明の化合物と類似した構造を有する化合物が多数報告されている。例えば、式（１）においてＲ^{2}が置換Ｃ$_{1}$～Ｃ$_{4}$アルキル基である誘導体がニトリックオキシド合成酵素阻害活性を有すると報告されている（国際特許公開ＷＯ９７１５５５５号明細書）。式（１）においてＲ^{2}が置換アルカノイル基である誘導体が脳神経細胞死抑制効果を有すると報告されている（国際特許公開ＷＯ９４１８１７２号明細書）。また、式（１）においてＲ^{2}が置換フェニルアルコキシ基である誘導体が抗高脂血症または動脈硬化に有効であると報告されている（国際特許公開ＷＯ９５２９１６３号明細書）。そして、式（１）においてＲ^{2}が置換アルコキシ基である誘導体が抗不整脈、抗高血圧または高虚血治療剤として有効であると報告されている（ヨーロッパ特許公開ＥＰ０３０６４４０号明細書、米国特許ＵＳ５２０２３４６号明細書）。しかし、いずれにおいても２０－ＨＥＴＥ産生酵素阻作用を有することについては報告されていない。
【０００４】
一方、イミダゾリルベンゾフェノン誘導体が２０－ＨＥＴＥ産生酵素阻作用を示すことを報告されていが（国際特許公開ＷＯ０１６８６１０号明細書）、活性あるいは物性は必ずしも満足できるものではない。
【０００５】
【発明が解決しようとする課題】
本発明は、腎臓、脳血管等の主要臓器における微小血管収縮又は拡張、或いは、細胞増殖惹起等に関与する２０－ＨＥＴＥの産生を阻害する薬剤を提供することを目的としている。
【０００６】
【課題を解決するための手段】
本発明者らは前記課題を解決する目的で鋭意探索研究した結果、ある特異な部分構造を有

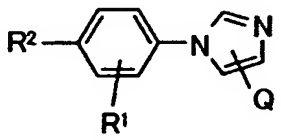
する芳香族化合物、特に様々な置換基を有する１－（４－置換フェニル）－１Ｈ－イミダゾール誘導体が意外にも選択的に２０－ＨＥＴＥの産生酵素の阻害作用を有することを見出し、本発明を完成した。

【０００７】

すなわち、本発明は、下記式（１）

【０００８】

【化３】



(1)

【０００９】

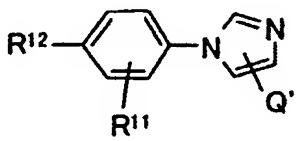
｛式中、Ｑは水素原子またはC_1～C_4アルキル基であり、R^1は、水素原子、C_1～C_6アルキル基、ハロゲン原子であり、R^2はC_1～C_{14}アルキル基、C_2～C_{14}アルカノイル基、モルホリノ基又は式R^3－Ｏ－［式中、R^3は、C_1～C_{14}アルキル基、C_2～C_{14}アルケニル基、C_3～C_{14}アルキニル基、C_3～C_{10}シクロアルキル基、１－フェニル－２－プロピニル基又は式R^4－Ａ－（式中、R^4はC_3～C_{10}シクロアルキル基、C_1～C_{10}アルコキシ基、C_2～C_{10}アルカノイル基、C_2～C_6アルコキシカルボニル基、ジオキソラニル基、C_1～C_6アルキル基で置換されたジオキソラニル基、オキサニル基、ジオキサニル基、C_1～C_6アルキル基で置換されたジオキサニル基、ベンゾジオキサニル基、ビシクロ［２．２．１］ヘプタン－２－イル基、C_1～C_6アルキルチオ基、ピロリジニル基、C_1～C_6アルキル基で置換されたピロリジニル基、ピペリジニル基、C_1～C_6アルキル基で置換されたピペリジニル基、モルホリノ基、４－C_2～C_6アルコキシカルボニルピペラジン－１－イル基、ピロリル基、ピリジル基、Ｎ，Ｎ－ジC_1～C_6アルキルアミノ基、Ｎ，Ｎ－ジC_1～C_6アルキルアミノC_1～C_6アルコキシ基、C_1～C_6アルコキシC_1～C_6アルコキシ基、フェノキシ基、フェニル基、「C_1～C_6アルキル基、C_1～C_6アルコキシ基、ハロゲン原子、フェニルエチル基、フェノキシ基、ニトリル及びメチルチオ基」から選ばれる基の１又は２個で置換されたフェニル基、ビフェニル基、フェニルチオ基、フリル基、チエニル基、チアゾリル基、C_1～C_6アルキル基で置換されたチアゾリル基、トルイジノ基、Ｎ－C_1～C_6アルキルトルイジノ基、ピロリドン－１－イル基であり、ＡはC_1～C_{10}アルキレン基である。）で示される基である。］で示される基である。｝で表されるイミダゾール誘導体又はその製薬学的に許容される塩を有効成分として含むことを特徴とする２０－ＨＥＴＥ産生酵素阻害剤である。

【００１０】

また、他の本発明は下記式（２）

【００１１】

【化４】



(2)

【００１２】

｛式中、Ｑ’は水素原子またはC_1～C_4アルキル基であり、R^{11}は、水素原子、C_1

～C_6アルキル基、ハロゲン原子であり、R^{12}はモルホリノ基又は式$R^{13}-O-$［式中、R^{13}は、C_3～C_{14}アルキニル基、C_3～C_{10}シクロアルキル基、1－フェニル－2－プロピニル基又は式$R^{14}-A'-$（式中、R^{14}はC_3～C_{10}シクロアルキル基、C_1～C_{10}アルコキシ基、C_2～C_{10}アルカノイル基、ジオキソラニル基、C_1～C_6アルキル基で置換されたジオキソラニル基、オキサニル基、ジオキサニル基、C_1～C_6アルキル基で置換されたジオキサニル基、ベンゾジオキサニル基、ビシクロ［2．2．1］ヘプタン－2－イル基、C_1～C_6アルキルチオ基、4－C_2～C_6アルコキシカルボニルピペラジン－1－イル基、ピロリル基、N，N－ジC_1～C_6アルキルアミノC_1～C_6アルコキシ基、C_1～C_6アルコキシC_1～C_6アルコキシ基、フリル基、チエニル基、ピロリドン－1－イル基であり、A'はC_1～C_{10}アルキレン基である。）で示される基である。］で示される基である。｝で表されるイミダゾール誘導体又はその製薬学的に許容される塩を提供するものである。

【００１３】

他の本発明は、上記のイミダゾール誘導体又はその製薬学的に許容される塩を有効成分とする医薬を提供するものである。

他の本発明は、上記のイミダゾール誘導体又はその製薬学的に許容される塩を有効成分とする腎疾患、脳血管疾患又は循環器疾患治療薬を提供するものである。

【００１４】

本発明において使用される用語が以下に定義される。

本発明において、「C_x～C_y」とは、その後に続く基がx～y個の炭素原子を有することを示す。

【００１５】

ハロゲン原子は、フッ素原子、塩素原子、臭素原子又はヨウ素原子であり、好ましくはフッ素原子、塩素原子又は臭素原子であり、より好ましくはフッ素原子又は塩素原子である。

C_1～C_{14}アルキル基は、炭素原子を1～14個有する直鎖状又は分枝状のアルキル基を意味し、C_1～C_8アルキル基が好ましい。C_1～C_8アルキル基としては、例えば、メチル基、エチル基、n－プロピル基、n－ブチル基、n－ヘキシル基、n－ヘプチル基、n－オクチル基、イソブチル基、sec－ブチル基、イソペンチル基、イソヘキシル基、3－メチルヘプチル基、3，3－ジメチルブチル基などがより好ましい

C_3～C_{10}シクロアルキル基は、炭素原子を3～10個有する環状アルキル基を意味し、例えば、シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基、シクロヘプチル基、シクロオクチル基などが挙げられる。中でも、シクロプロピル基、シクロペンチル基、シクロヘキシル基が好ましい。

【００１６】

C_2～C_{14}アルケニル基は、少なくとも1つの二重結合及び炭素原子を2～14個有する直鎖状又は分枝状のアルケニル基を意味し、例えば、エテニル基、プロペニル基、2－ブテニル基、3－メチル－2－ブテニル基、ペンテニル基、2－メチル－2－ペンテニル基、ヘキセニル基、2，4－ヘキサジエニル基、ヘプテニル基、オクテニル基、3，7－ジメチル－2，6－オクタジエニル基などが挙げられる。

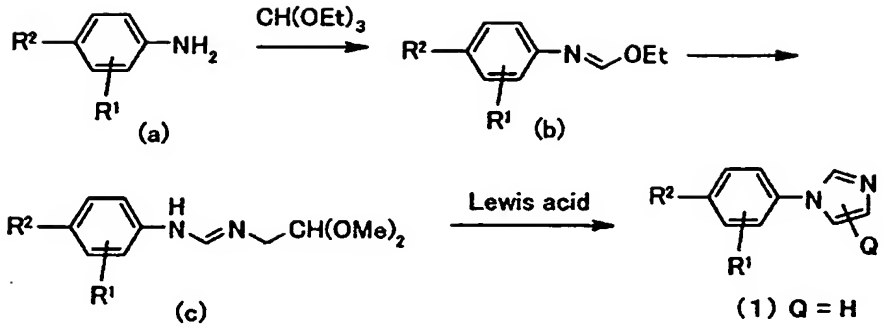
C_2～C_{14}アルキニル基は、少なくとも1つの三重結合及び炭素原子を2～6個有する直鎖状又は分枝状のアルキニル基を意味し、例えば、エチニル基、2－プロピニル基、ブチニル基、5－ペンチニル基、ヘキセニル基、ヘプチニル基、オクチニル基などが挙げられる。

【００１７】

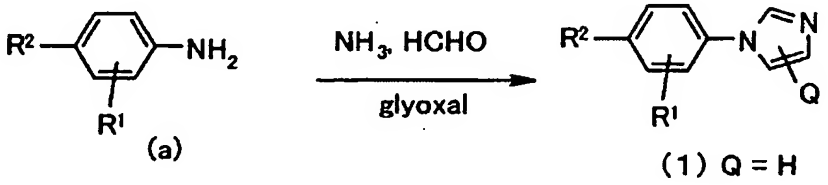
C_1～C_{10}アルコキシ基は、炭素原子を1～10個有する直鎖状又は分枝状のアルコキシ基を意味し、C_1～C_8アルコキシ基が好ましい。C_1～C_8アルコキシ基としては、例えば、メトキシ基、エトキシ基、プロポキシ基、イソプロポキシ基、n－ブトキシ基、イソブトキシ基、tert－ブトキシ基、ヘキシルオキシ基、ヘプチルオキシ基などが挙げられる。

【００１８】
C_1～C_6アルコキシC_1～C_6アルコキシ基は、C_1～C_6アルコキシ基とC_1～C_6アルコキシ基が複合した形態を有するものであり、C_1～C_4アルコキシC_1～C_4アルコキシ基が好ましい。中でも、メトキシエトキシ基、ｎ－ブトキシエトキシ基などがより好ましい。
C_2～C_6アルコキシカルボニル基は、炭素原子を２～５個有する直鎖状又は分枝状のアルコキシ基と１個のカルボニル基（－ＣＯ－）が複合した形態を有するものであり、C_2～C_4アルコキシカルボニル基が好ましい。中でも、メトキシカルボニル基、エトキシカルボニル基などがより好ましい。
【００１９】
ジオキソラニル基は、ヘテロ原子として酸素原子を２個有する飽和五員環（ジオキソラン）、好ましくは１，３－ジオキソランの環から水素を除いて誘導される１価の基を意味する。
オキサニル基は、ヘテロ原子として酸素原子を１個有する飽和六員環の形態を有するもので、２－オキサニル基、３－オキサニル基を含む。
ジオキサニル基は、ヘテロ原子として酸素原子を２個有する飽和六員環（ジオキサン）、好ましくは１，３－ジオキサンの環から水素を除いて誘導される１価の基を意味する。C_1～C_6アルキル基で置換されたジオキサニル基は、その基の環がC_1～C_6アルキル基で置換されていてもよく、例えば５，５－ジメチル－１，３－ジオキサン－２－イル基などである。
【００２０】
C_1～C_6アルキルチオ基は、炭素原子を１～６個有する直鎖状又は分枝状のアルキル基と１個のチオ基（－Ｓ－）が複合した形態を有しており、C_1～C_4アルキルチオ基が好ましい。例えば、メチルチオ基、エチルチオ基などがより好ましい。
【００２１】
ピロリジニル基は、ピロリジンの環状の窒素原子又は炭素原子上から水素原子を除いて誘導される１価の基を意味し、例えば、１－ピロリジニル基、２－ピロリジニル基、３－ピロリジニル基などが挙げられる。C_1～C_6アルキル基で置換されたピロリジニル基は、その基上の少なくとも１つの水素原子がC_1～C_6アルキル基、好ましくはC_1～C_4アルキル基によって置換されたピロリジニル基であり、例えば、Ｎ－メチルピロリジン－２－イル基などが挙げられる。
ピペリジニル基は、ピペリジンの炭素原子上から水素原子を除いて誘導される１価の基を意味する。C_1～C_6アルキル基で置換されたピペリジニル基は、その基の窒素原子がC_1～C_6アルキル基によって置換されたピペリジニル基であり、例えば、Ｎ－メチルピペリジン－２－イル基、Ｎ－メチルピペリジン－３－イル基などが挙げられる。
４－C_2～C_6アルコキシカルボニルピペラジン－１－イル基は、ピペラジンの４位の窒素原子がC_2～C_6アルコキシカルボニル基で修飾され、１位の窒素原子上から水素原子を除いて誘導される１価の基を意味する。
モルホリノ基は、モルホリンの窒素原子上から水素原子を除いて誘導される１価の基を意味する。
【００２２】
フリル基は、２－フリル基、３－フリル基を含む。
チエニル基は、２－チエニルル基、３－チエニル基を含む。
チアゾリル基は、２－チアゾリル基、４－チアゾリル基、５－チアゾリル基を含む。また、C_1～C_6アルキル基で置換されたチアゾリル基は、その環上の少なくとも１つの水素原子がC_1～C_6アルキル、好ましくはC_1～C_4アルキル基、より好ましくはメチル基によって置換されたチアゾリル基であり、例えば４－メチルチアゾール－５－イル基などが挙げられる。
ピリジル基は、２－ピリジル基、３－ピリジル基、４－ピリジル基を含む。　ピロリル基は、１－ピロリル基、２－ピロリル基、３－ピロリル基を含み、１－ピロリル基（Ｎ－ピ

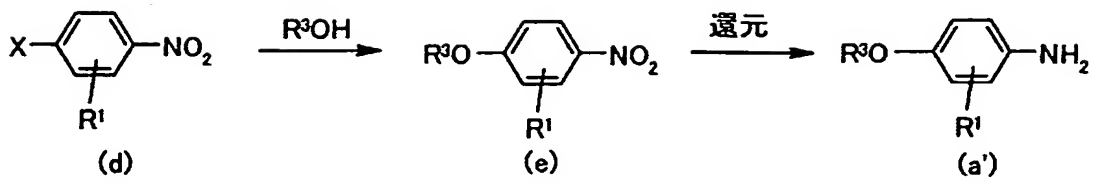
ロリル基）が好ましい。
【００２３】
Ｎ，Ｎ－ジＣ$_1$～Ｃ$_6$アルキルアミノＣ$_1$～Ｃ$_6$アルコキシ基は、Ｎ，Ｎ－ジＣ$_1$～Ｃ$_6$アルキルアミノ基とＣ$_1$～Ｃ$_6$アルコキシ基が複合した形態を有するものであり、例えば、Ｎ，Ｎ－ジエチルアミノエトキシ基などが挙げられる。
ピロリドン－１－イル基は２－ピロリドン－１－イル基、３－ピロリドン－１－イル基を含む。
【００２４】
Ａ及びＡ’で定義されるＣ$_1$～Ｃ$_{10}$アルキレン基は、炭素原子を１～１０個有する直鎖状又は分枝状のアルキレン基を意味し、例えば、メチレン基、メチルメチレン基、エチレン基、プロピレン基、ヘプチレン基、２，２－ジメチルプロピレン基、ヘキシレン基などが挙げられる。
【００２５】
そして、上記した各種の基は、上記に挙げた置換された形態の他にも、その基上の少なくとも１つの水素原子が、例えばフッ素原子、塩素原子、臭素原子、ヨウ素原子等のハロゲン原子；ニトロ基；アミノ基；ヒドロキシ基；チオール基；ホルミル基；カルボキシル基；シアノ基；カルバモイル基；メチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、ｓｅｃ－ブチル基、ｔｅｒｔ－ブチル基、ペンチル基、イソペンチル基、ネオペンチル基、ｔｅｒｔ－ペンチル基等のアルキル基；フェニル基、ナフチル基、ビフェニル基、アントラニル基等のアリール基；ピロリル基、ピリジル基、チエニル基等の複素環基；メトキシカルボニル基、エトキシカルボニル基等のアルコキシカルボニル基；アセチル基、ベンゾイル基等のアシル基；メトキシ基、エトキシ基、プロポキシ基等のアルコキシ基；メチルチオ基、エチルチオ基、プロピルチオ基等のアルキルチオ基；等の非水素原子又は基によって置換されていてもよい。なお、これらの置換基中の炭素原子数は、上記したｘ又はｙには含まれない。
【００２６】
また、製薬学的に許容される塩とは、アルカリ金属類、アルカリ土類金属類、アンモニウム、アルキルアンモニウムなどとの塩、鉱酸又は有機酸との塩であり、例えば、ナトリウム塩、カリウム塩、カルシウム塩、アンモニウム塩、アルミニウム塩、トリエチルアンモニウム塩、酢酸塩、プロピオン酸塩、酪酸塩、ぎ酸塩、トリフルオロ酢酸塩、マレイン酸塩、酒石酸塩、クエン酸塩、ステアリン酸塩、コハク酸塩、エチルコハク酸塩、ラクトビオン酸塩、グルコン酸塩、グルコヘプトン酸塩、安息香酸塩、メタンスルホン酸塩、エタンスルホン酸塩、２－ヒドロキシエタンスルホン酸塩、ベンゼンスルホン酸塩、パラトルエンスルホン酸塩、ラウリル硫酸塩、リンゴ酸塩、アスパラギン酸塩、グルタミン酸塩、アジピン酸塩、システインとの塩、Ｎ－アセチルシステインとの塩、塩酸塩、臭化水素酸塩、リン酸塩、硫酸塩、よう化水素酸塩、ニコチン酸塩、シュウ酸塩、ピクリン酸塩、チオシアン酸塩、ウンデカン酸塩、アクリル酸ポリマーとの塩、カルボキシビニルポリマーとの塩などを挙げることができる。
【００２７】
【発明の実施の形態】
本発明化合物（１）は、例えば以下に示す方法によって合成することができる。
【００２８】
【化５】



【００２９】
製造法１；Ｊ．Ｈｅｔｅｒｏｃｙｃｌｉｃ Ｃｈｅｍ．，第２５巻，１６４９項（１９８８）を参照にアニリン誘導体（ａ）を酢酸または塩酸等の酸触媒の存在下或いは非存在下に、オルトギ酸トリメチル、オルトギ酸トリエチル等のオルトギ酸エステル類と、反応させ、イミノエーテル誘導体（ｂ）を得る。反応温度は室温から１５０℃、好ましくは７０～１００℃で反応時間は２～７２時間である。次に、イミノエーテル誘導体（ｂ）を適当な溶媒中（メタノール、エタノール、プロパノール、テトラヒドロフラン、ジオキサン、トルエン、塩化メチレン、クロロホルム、アセトニトリル、酢酸エチル、ジメチルスルホキシド、ジメチルホルムアミド等）アミノアセトアルデヒドジメチルアセタールと反応させホルムアミジン誘導体（ｃ）を得る。この時の反応温度は室温～１５０℃、好ましくは７０～１００℃であり、反応時間は２～２４時間である。次に、ホルムアミジン誘導体（ｃ）を適当な溶媒中（エーテル、テトラヒドロフラン、ジメトキシエタン、ジオキサン等）にルイス酸あるいは酸触媒（四塩化チタン、トリフルオロボランエーテラート、酢酸等）の共存下反応させ、本発明化合物（１）を合成することができる（式中R^1、R^2は前記と同義である）。また、この方法で合成した本発明化合物（１）のR^2を相互に変換することによって他の本発明化合物（１）に導くこともできる。
【００３０】
【化６】



【００３１】
製造法２；化合物（１）はアニリン誘導体（ａ）から直接合成することもできる。すなわち、アニリン誘導体とアンモニア、ホルムアルデヒド、そしてグリオキサールを１：１：１：１の比率で混合し水またはアルコール／水の混合溶媒中にて、反応温度は室温～１５０℃、好ましくは７０～１２０℃で反応することによって本発明化合物（１）を合成することができる（式中R^1、R^2は前記と同義である）。
【００３２】
【化７】

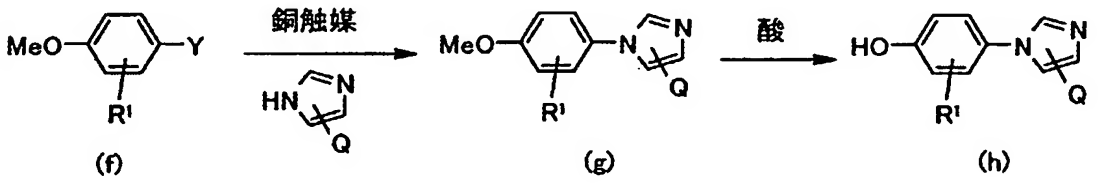


【００３３】

製造法３；合成中間体であるアニリン誘導体（ａ'）（Ｒ^{2}が置換アルコキシ基すなわちＲ^{2}＝Ｒ^{3}Ｏを示す）を以下のようにして合成することができる。すなわち、ニトロベンゼン誘導体（ｄ）（式中Ｘはフッ素、塩素等の脱離基を示し、他の記号は前記と同義である）を適当な溶媒中（メタノール、エタノール、プロパノール、テトラヒドロフラン、ジオキサン、トルエン、塩化メチレン、クロロホルム、アセトニトリル、酢酸エチル、ジメチルスルホキシド、ジメチルホルムアミド等）必要に応じて塩基（トリエチルアミン、Ｎ，Ｎ－ジイソプロピルエチルアミン、ピリジン、炭酸カリウム、炭酸カルシウム、炭酸セシウム、水素化ナトリウム、ナトリウムメトキシド、ｔ－ブトキシカリウム等）の存在下、対応する種々のアルコール類と反応し化合物（ｅ）を製造することができる。この時反応温度は０℃～８０℃、好ましくは０℃～室温で、反応時間は１～１２時間、好ましくは１～２時間である。次に、化合物（ｅ）を適当な溶媒中（メタノール、エタノール、プロパノール、テトラヒドロフラン、ジオキサン、トルエン、塩化メチレン、クロロホルム、アセトニトリル、酢酸エチル等）、還元剤（パラジウム活性炭／水素雰囲気下、パラジウム活性炭／ヒドラジン水和物、パラジウム活性炭／ぎ酸アンモニウム、塩化スズ（ＩＩ）１水和物、鉄／塩化アンモニウム、ラネーニッケル／ヒドラジン水和物等、好ましくはパラジウム活性炭／水素雰囲気下）を用いてニトロ基を還元することでアニリン誘導体（ａ'）を製造することができる。反応温度は室温～１５０℃、好ましくは室温～１００℃で、反応時間は１時間～２４時間である。

【００３４】

【化８】

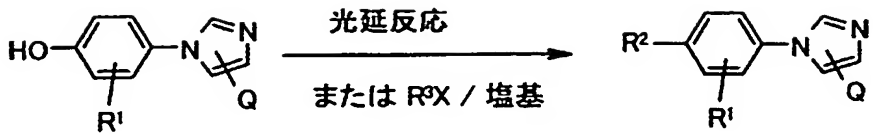


【００３５】

製造法４；化合物（１）は中間体（ｈ）を経て以下の様にして製造することができる。フェニルボロン酸またはハロゲン化フェニル誘導体（ｆ）（式中ＹはＢ（ＯＨ）$_{2}$またはハロゲン原子を表し、その他の記号は前記と同義である）を適当な溶媒中（メタノール、エタノール、プロパノール、テトラヒドロフラン、ジオキサン、トルエン、塩化メチレン、クロロホルム、アセトニトリル、酢酸エチル、ジメチルスルホキシド、ジメチルホルムアミド等）で銅触媒（［Ｃｕ（ＯＨ）ＴＭＥＤＡ］$_{2}$Ｃｌ$_{2}$、（ＣｕＯＴｆ）$_{2}$ｂｅｎｚｅｎｅ等）存在下、好ましくは酸素雰囲気下でイミダゾール誘導体と縮合し中間体（ｇ）を製造することができる［Ｏｒｇａｎｉｃ　Ｌｅｔｔ．，第２巻，１２３７項（２０００）］。反応温度は室温が好ましく、反応時間は１２～２４時間である。次いで、中間体（ｇ）を４８％臭化水素中１００℃～１５０℃で反応し中間体化合物（ｈ）を製造することができる。反応時間は１２時間～７２時間、好ましくは１２時間～２４時間である。

【００３６】

【化９】



(g) (1)

【００３７】
次に、４－（イミダゾール－１－イル）－フェノール誘導体（ｈ）と対応する種々のアルコールを光延反応（Ｏｒｇ．　Ｒｅａｃｔｉｏｎｓ，第４２巻，第３３５項）を利用し製造することができる。すなわち、化合物（ｈ）を適当な溶媒（テトラヒドロフラン、ジオキサン、トルエン、塩化メチレン、クロロホルム、アセトニトリル、酢酸エチル、ジメチルスルホキシド、ジメチルホルムアミド等）中で、ホスフィン試薬（トリフェニルホスフィン、トリブチルホスフィンやジフェニル－２－ピリジルホスフィン等）、ジアゾ試薬（ジエチルアゾジカルボキシレートやジ－ｔｅｒｔ－ブチルアゾジカルボキシレート等）、及び対応する種々のアルコール類とを、０℃～室温、好ましくは室温にて２～１２時間反応し、本発明化合物（１）（式中記号は前記と同意義である。）を製造することができる。或いは、種々のハロゲン化アルキル類（R^3X、Ｘはハロゲンを表し、その他の記号は前記と同義である）と、適当な溶媒（アセトン、ジメチルホルムアミド、テトラヒドロフラン、エーテル等）中適当な塩基（トリエチルアミン、Ｎ，Ｎ－ジイソプロピルエチルアミン、ピリジン、炭酸カリウム、炭酸カルシウム、炭酸セシウム、水素化ナトリウム、ナトリウムメトキシド、ｔ－ブトキシカリウム等）の存在下、で、０℃～室温、好ましくは室温にて２～２４時間反応し、R^2がR^3Oである本発明化合物（１）を製造することができる。
【００３８】
本発明化合物及びその製薬学的に許容される塩は、経口又は非経口的に投与することができる。その投与剤型は錠剤、カプセル剤、顆粒剤、散剤、粉剤、トローチ剤、軟膏剤、クリーム剤、乳剤、懸濁剤、坐剤、注射剤などであり、いずれも慣用の製剤技術（例えば、第１４改正日本薬局方に規定する方法）によって製造することができる。これらの投与剤型は、患者の症状、年齢及び治療の目的に応じて適宜選択することができる。各種剤型の製剤の製造においては、常用の賦形剤（例えば、結晶セルロース、デンプン、乳糖、マンニトールなど）、結合剤（例えば、ヒドロキシプロピルセルロース、ポリビニルピロリドンなど）、滑沢剤（例えば、ステアリン酸マグネシウム、タルクなど）、崩壊剤（例えば、カルボキシメチルセルロースカルシウムなど）などを用いることができる。
【００３９】
本発明に係る化合物並びにその製薬学的に許容される塩の投与量は、成人を治療する場合で１日１～２０００ｍｇであり、これを１日１回又は数回に分けて投与する。この投与量は、患者の年齢、体重及び症状によって適宜増減することができる。
【００４０】
【発明の効果】
本発明に係る化合物及びその製薬学的に許容される塩は、優れた２０－ＨＥＴＥ産生阻害作用を有し、溶解度などの物性的にも優れるものである。従って、本発明に係る化合物は、ヒト及び動物における２０－ＨＥＴＥが関わる疾病、例えば各種腎疾患、脳血管疾患、各種循環器疾患治療薬として有用である。
【００４１】
【実施例】
以下、実施例を挙げて本発明を更に詳しく説明する。
実施例１
１－［４－プロピルフェニル］－イミダゾール塩酸（化合物１０８）の製造
４－プロピルアニリン　（２．０３ｇ，　０．０１５０ｍｏｌ）とオルト蟻酸トリエチル

（４．９９ｇ，　０．３３７ｍｏｌ）の混合物を１００℃で７時間撹拌した。室温に冷却した後に、反応液にメタノール　（１５ｍＬ）とアミノアセトアルデヒドジメチルアセタール（５．６９ｇ，　０．０５４１ｍｏｌ）を加え、室温にて３０分撹拌し、さらに１００℃で４時間撹拌した。室温に冷却した後に、反応液を濃縮して得られた残査にジメトキシエタン（２０ｍＬ）と１Ｍ四塩化チタン－トルエン溶液　（２１ｍＬ，　０．０２１ｍｏｌ）を加え室温にて１時間さらに加熱還流下で４時間撹拌した。室温に冷却した後に、反応液に水酸化ナトリウム水溶液を加え、クロロホルムで抽出した。有機層を硫酸マグネシウムで乾燥し、濃縮した。得られた残査をシリカゲルクロマトグラフィー（クロロホルム－メタノール＝９７：３）で精製し１－［４－プロピルフェニル］－イミダゾール（２．０ｇ）を褐色油状物として得た。生成物に４Ｎ塩酸－酢酸エチル溶液を加え、酢酸エチル－クロロホルムの混合溶媒から再結晶し、無色粉末状の標題化合物　（１．３８ｇ，　４１．２％）を得た。融点１５５．５－１５７．０℃

【００４２】

実施例２

｛２－［２－（４－イミダゾール－１－イル－フェノキシ）－エトキシ］－エチル｝－ジメチルアミン２塩酸（化合物１１６）の製造

水素化ナトリウム　（６０％　ｏｉｌ，　１．０ｇ，　０．２６ｍｏｌ）のジメチルホルムアミド　（３．０ｍｌ）懸濁液に氷冷下、Ｎ，Ｎ－ジメチルアミノエチルオキシエタノール　（２．３ｇ，　０．２６ｍｏｌ）のジメチルホルムアミド溶液　（５ｍｌ）を滴下し、１０分間撹拌した。この反応混合物に４－フルオロニトロベンゼン　（３ｇ，　０．０２１ｍｏｌ）のジメチルホルムアミド溶液　（１０ｍＬ）を滴下し、室温にて２時間撹拌した。反応混合物に水を加え、酢酸エチルで抽出し、有機層を飽和食塩水洗浄後、$MgSO_4$乾燥し、減圧下濃縮しジメチル－｛２－［２－（４－ニトロフェノキシ）－エトキシ］－エチル｝アミン　（５．９ｇ）を得た。上記で得た化合物をメタノール　（１００ｍＬ）に溶解し、１０％パラジウム活性炭　（０．６ｇ）を加え、水素雰囲気下で室温にて３時間撹拌した。ＴＬＣ分析により原料の消失を確認した後に、セライトを用いて不溶物を濾過し、濾液を濃縮してアニリン誘導体　（５．０ｇ）を褐色油状物として得た。次に、このアニリン誘導体にオルトギ酸トリエチル　（１０ｍＬ，　０．０６０ｍｏｌ）を加えて１００℃で２０時間撹拌した。室温に冷却した後に、反応液にメタノール（８０ｍＬ）とアミノアセトアルデヒドジメチルアセタール　（６．８ｍＬ，　０．０６３ｍｏｌ）を加え、１００℃で１．５時間撹拌した。反応液を濃縮して得られた残査にジメトキシエタン　（３０ｍＬ）と１Ｍ四塩化チタン－トルエン溶液　（２５ｍＬ，　０．０２５ｍｏｌ）を加え加熱還流下で５時間撹拌した。室温に冷却した後に、反応液に水酸化ナトリウム水溶液を加えた。析出した不溶物を濾過した後に濾液を酢酸エチルで抽出した。有機層を飽和食塩水洗浄後、硫酸マグネシウムで乾燥し、濃縮した。得られた残査をＮＨ型シリカゲルクロマトグラフィー（ヘキサン－酢酸エチル＝１：２）で精製し　｛２－［２－（４－イミダゾール－１－イル－フェノキシ）－エトキシ］－エチル｝－ジメチルアミン（０．４０ｇ，　６．９％）を油状物として得た。生成物をエーテルに溶解し、４Ｍ塩酸－酢酸エチル溶液を加え、濃縮して析出した粉末を酢酸エチルで洗い、標題化合物を得た（４２８ｍｇ）。融点１７４．０－１７９．０℃

【００４３】

実施例３

１－［４－プロピルオキシフェニル］－イミダゾールトルエンスルホネート（化合物９４）の製造

４－（イミダゾール－１－イル）フェノール　（１．０ｇ，　６．２５ｍｍｏｌ）、プロパノール　（５６３ｍｇ，　９．３８ｍｍｏｌ）、トリフェニルホスフィン　（２．４６ｇ，　９．３８ｍｍｏｌ）及びテトラヒドロフラン　（２０ｍＬ）の混合物にジエチルアゾジカルボキシレート（１．４８ｍＬ，　９．３８ｍｍｏｌ）を加え、室温にて６時間撹拌した。反応混合物を濃縮した後に、酢酸エチル（４０ｍＬ）を加え、１Ｍ塩酸（２０ｍＬ）で抽出した。水層を５Ｍ水酸化ナトリウムで中和した後に、酢酸エチルで抽出した。

有機層を飽和食塩水洗浄後、硫酸マグネシウムで乾燥し、濃縮した。得られた残査をＮＨ型シリカゲルクロマトグラフィー（ヘキサン－酢酸エチル＝１：２）で精製し１－［４－プロピルオキシフェニル］－１Ｈ－イミダゾール　（１．１７ｇ，　９２％）を無色油状物として得た。これをエタノールに溶解しｐ－トルエンスルホン酸１水和物　（１．１ｇ，　５．７８ｍｍｏｌ）のエタノール溶液を加え析出した結晶を濾過し、無色粉末状の標題化合物　（１．９８ｇ，　８５％）を得た。融点１４８．０－１５０．０℃

【００４４】

実施例４

１－［４－ブトキシフェニル］－２－メチル－イミダゾールトルエンスルホネート（化合物１１７）の製造

（１）４－メトキシフェニルボレート　（３．７ｇ，　２４．４ｍｍｏｌ）と１－Ｈ－２－メチルイミダゾール　（１．０ｇ，　１２．２ｍｍｏｌ）、塩化メチレン　（４８ｍＬ）の混合物に、［Ｃｕ（ＯＨ）ＴＭＥＤＡ］$_2$Ｃｌ$_2$（０．５７ｇ，　１．２２ｍｍｏｌ）を加え、酸素雰囲気下、室温にて１８時間撹拌した。反応混合物を濾過して不溶物を除いた後、濾液を濃縮した。得られた残査をＮＨ型シリカゲルクロマトグラフィー（ヘキサン－酢酸エチル＝４：１）で精製し、１－［４－メトキシフェニル］－２－メチル－イミダゾール　（２．３５ｇ）を得た。

【００４５】

（２）１－［４－メトキシフェニル］－２－メチル－イミダゾール　（２．０ｇ）と４８％臭化水素　（２０ｍＬ）の混合物を１００℃で１６時間反応した。反応液を室温に冷却した後に、６Ｍ水酸化ナトリウムで中和後析出した結晶を濾過し、４－（２－メチル－イミダゾール－１－イル）フェノール　（０．７５ｇ，　４０％）を得た。

【００４６】

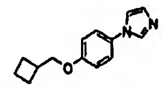
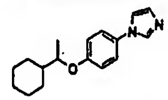
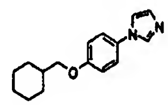
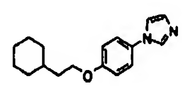
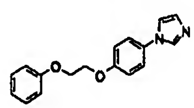
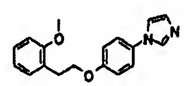
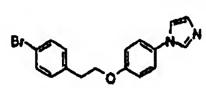
（３）４－（２－メチル－イミダゾール－１－イル）フェノール　（０．２０ｇ，　１．２ｍｍｏｌ）とジメチルホルムアミド　（２ｍＬ）溶液に、１－イオド－ｎ－ブタン　（０．２５ｇ，　１．３８ｍｍｏｌ）と炭酸カリウム　（０．１９ｇ，　１．３８ｍｍｏｌ）を加え、室温で６４時間撹拌した。反応液に水を加え、ヘキサン－酢酸エチル＝１：１の混合溶媒で抽出した。有機層を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、濃縮した。得られた残査をＮＨ型シリカゲルクロマトグラフィー（ヘキサン－酢酸エチル＝４：１）で精製し、１－［４－ブトキシフェニル］－２－メチル－イミダゾール　（０．１７ｇ，　６４％）を得た。これをエタノールに溶解しｐ－トルエンスルホン酸１水和物のエタノール溶液を加え、析出した結晶を濾過し、無色粉末状の標題化合物　（０．１８ｇ，　３９％）を得た。融点１４８．０－１４９．０℃

【００４７】

各々対応する出発原料を用いて実施例１～４と同様な反応操作を行うことにより、表１に示す化合物を合成した。尚、表１には実施例１～４で合成した化合物を併せて標記した。

【００４８】

【表１】

化合物番号	構造式	^{1}H NMR (300MHz, $CDCl_3$) spectra and melting points	抑制率 % at 0.1uM	IC_{50} (nM)
化合物 1		δ 1.86-2.04 (m, 4H), 2.15 (m, 2H), 2.79 (m, 1H), 3.96 (d, J = 6.7Hz, 2H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	85.8	
化合物 2		δ 1.03-1.22 (m, 4H), 1.27 (d, J = 6.1Hz, 3H), 1.58-1.80 (m, 6H), 1.93 (m, 1H), 4.15 (d, J = 6.1Hz, 1H), 6.95 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	79.6	
化合物 3		δ 1.04-1.19 (m, 2H), 1.20-1.39 (m, 3H), 1.62-1.92 (m, 6H), 3.78 (d, J = 6.2Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	84.4	
化合物 4		δ 1.00 (m, 2H), 1.19-1.38 (m, 3H), 1.45-1.80 (m, 8H), 4.03 (t, J = 6.7Hz, 2H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	94.1	
化合物 5		δ 4.37 (s, 4H), 6.95-6.98 (m, 3H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.22 (s, 1H), 7.26-7.33 (m, 3H), 7.77 (s, 1H).	96.9	
化合物 6		δ 3.14 (t, J = 7.5Hz, 2H), 3.86 (s, 3H), 4.19 (t, J = 7.5Hz, 2H), 6.88-6.95 (m, 2H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.18-7.13 (m, 6H), 7.76 (s, 1H).	97.3	
化合物 7		δ 3.07 (t, J = 6.7Hz, 2H), 4.18 (t, J = 6.7Hz, 2H), 6.96 (m, J_{AB} = 9.0Hz, 2H), 7.16-7.20 (m, 4H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.45 (m, J_{AB} = 8.2Hz, 2H), 7.75 (s, 1H).	100.8	

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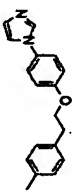
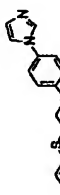
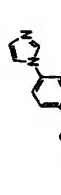
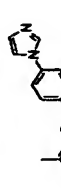
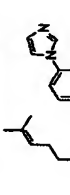
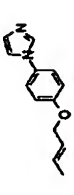
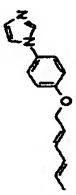
化合物 8		δ 2.34 (s, 3H), 3.09 (t, J = 7.1Hz, 2H), 4.18 (t, J = 7.1Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.13-7.20 (m, 4H), 7.27 (m, J_{AB} = 9.0Hz, 2H), 7.75 (s, 1H).	105.9
化合物 9		δ 3.32 (t, J = 6.9Hz, 2H), 4.18 (t, J = 6.9Hz, 2H), 6.93 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.19 (s, 1H), 7.21-7.35 (m, 5H), 7.43 (m, J_{AB} = 9.0Hz, 2H), 7.75 (s, 1H).	99.0
化合物 10		δ 2.56 (t, J = 2.5Hz, 1H), 4.75 (d, J = 2.5Hz, 2H), 7.08 (m, J_{AB} = 9.0Hz, 2H), 7.10 (s, 1H), 7.19 (s, 1H), 7.33 (m, J_{AB} = 9.0Hz, 2H), 7.77 (s, 1H).	42.9
化合物 11		δ 1.77 (s, 3H), 1.82 (s, 3H), 4.55 (d, J = 6.7Hz, 2H), 5.50 (m, 1H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.78 (s, 1H).	93.8
化合物 12		δ 1.62 (s, 3H), 1.69 (s, 3H), 1.82 (s, 3H), 2.15 (m, 4H), 4.54 (d, J = 6.8Hz, 2H), 5.12 (m, 1H), 5.51 (t, J = 6.8Hz, 1H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	91.9
化合物 13		δ 1.78 (dd, J = 1.4, 6.2Hz, 3H), 4.50 (dt, J = 1.2, 5.9Hz, 2H), 5.69-5.96 (m, 2H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	104.9
化合物 14		δ 1.78 (d, J = 6.8Hz, 3H), 4.58 (d, J = 6.2Hz, 2H), 5.73-5.81 (m, 2H), 6.10 (m, 1H), 6.35 (dd, J = 10.7, 15.7Hz, 3H), 6.99 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	98.1

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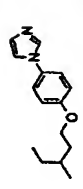
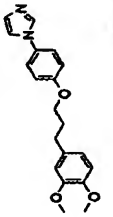
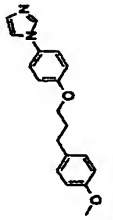
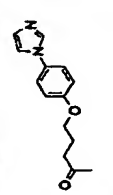
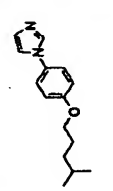
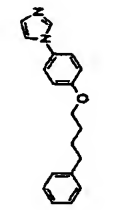
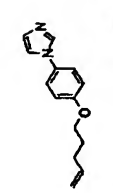
【表３】

化合物 15		δ 0.92 (d, J = 7.5Hz, 3H), 0.96 (d, J = 6.4Hz, 3H), 1.26 (m, 1H), 1.40 (m, 1H), 1.62 (m, 2H), 1.84 (m, 1H), 4.02 (m, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	104.0
化合物 16		δ 2.11 (tt, J = 6.2, 7.2Hz, 2H), 2.78 (t, J = 7.2Hz, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 3.99 (t, J = 6.2Hz, 2H), 6.74–6.82 (m, 3H), 6.85 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	97.4
化合物 17		δ 2.10 (tt, J = 8.4, 7.2Hz, 2H), 2.77 (t, J = 7.2Hz, 2H), 3.78 (s, 3H), 3.98 (t, J = 6.4Hz, 2H), 6.85 (m, J_{AB} = 8.5Hz, 2H), 6.96 (m, J_{AB} = 9.0Hz, 2H), 7.13 (m, J_{AB} = 8.5Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	99.5
化合物 18		δ 2.09 (tt, J = 6.1, 7.2Hz, 2H), 2.19 (s, 3H), 2.68 (t, J = 7.2Hz, 2H), 4.02 (t, J = 6.1Hz, 2H), 6.96 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	105.4
化合物 19		δ 0.94 (d, J = 6.5Hz, 6H), 1.37 (m, 2H), 1.63 (m, 2H), 1.81 (m, 2H), 3.98 (t, J = 6.5Hz, 2H), 6.98 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	85.7
化合物 20		δ 1.80–1.90 (m, 4H), 2.71 (t, J = 7.1Hz, 2H), 4.00 (t, J = 6.1Hz, 2H), 6.95 (m, J_{AB} = 9.0Hz, 2H), 7.18–7.32 (m, 9H), 7.78 (s, 1H).	94.0
化合物 21		δ 1.91 (m, 2H), 2.25 (m, 2H), 4.01 (t, J = 6.4Hz, 2H), 5.01–5.12 (m, 2H), 5.85 (m, 1H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.78 (s, 1H).	99.2

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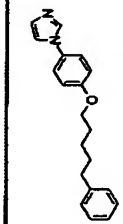
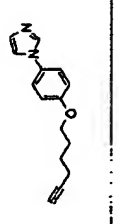
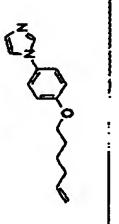
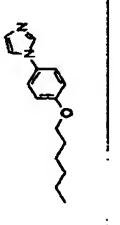
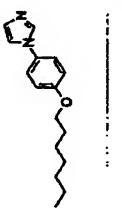
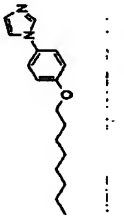
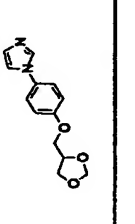
化合物 22		δ 1.47–1.89 (m, 6H), 2.66 (t, J = 7.5Hz, 2H), 3.98 (t, J = 6.5Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.18–7.20 (m, 5H), 7.26–7.31 (m, 4H), 7.76 (s, 1H).	88.5
化合物 23		δ 1.74 (m, 2H), 1.92 (m, 2H), 1.98 (t, J = 2.6Hz, 2H), 2.30 (dt, J = 2.8, 7.0Hz, 2H), 4.03 (t, J = 6.3Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	99.5
化合物 24		δ 1.60 (m, 2H), 1.83 (quint, J = 7.0Hz, 2H), 2.14 (q, J = 7.0Hz, 2H), 4.00 (t, J = 6.5Hz, 2H), 4.98–5.08 (m, 2H), 5.77–5.91 (m, 1H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	99.1
化合物 25		δ 0.92 (t, J = 7.0Hz, 3H), 1.33–1.39 (m, 4H), 1.47 (m, 2H), 1.81 (m, 2H), 3.99 (t, J = 6.7Hz, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	98.8
化合物 26		δ 0.90 (t, J = 6.8Hz, 3H), 1.25–1.45 (m, 8H), 1.81 (quint, J = 6.8Hz, 2H), 3.99 (t, J = 6.8Hz, 2H), 6.98 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	91.5
化合物 27		δ 0.89 (t, J = 6.8Hz, 3H), 1.23–1.54 (m, 10H), 1.79 (quint, J = 6.8Hz, 2H), 3.99 (t, J = 6.8Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	68.0
化合物 28		δ 3.89 (m, 1H), 3.99–4.18 (m, 3H), 4.46 (dt, J = 5.5, 7.7Hz, 2H), 4.95 (s, 1H), 5.11 (s, 1H), 7.01 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.31 (m, J_{AB} = 9.0Hz, 2H), 7.77 (s, 1H).	80.3

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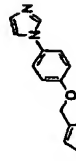
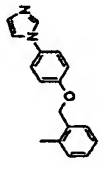
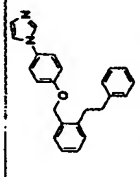
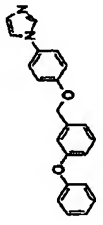
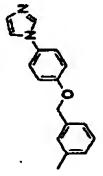
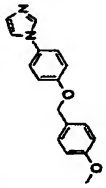
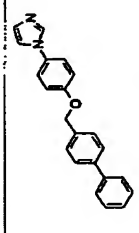
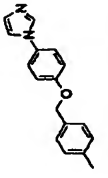
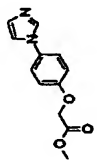
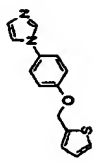
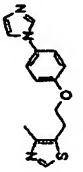
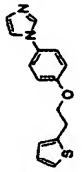
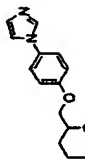
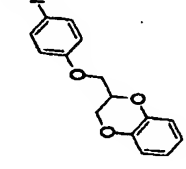
【表５】

化合物 29		δ 5.05 (s, 2H), 6.40 (dd, J = 1.9, 3.1Hz, 1H), 6.47 (d, J = 3.1Hz, 1H), 7.07 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 9.0Hz, 2H), 7.48 (d, J = 1.9Hz, 1H), 7.77 (s, 1H).	64.1
化合物 30		δ 1.26-2.03 (m, 13H), 3.76 (d, J = 6.5Hz, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	102.2
化合物 31		δ 0.92 (t, J = 7.0Hz, 3H), 1.26-1.39 (m, 4H), 1.59 (m, 2H), 1.97 (m, 2H), 4.74 (m, 1H), 7.11 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 9.0Hz, 2H), 7.77 (s, 1H).	87.1
化合物 32		δ 5.18 (s, 2H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.26 (m, 1H), 7.32 (m, J_{AB} = 8.9Hz, 2H), 7.38 (m, 1H), 7.74 (d, J = 7.6Hz, 1H), 7.80 (d, J = 7.9Hz, 1H), 7.77 (s, 1H).	108.3
化合物 33		δ 5.17 (s, 2H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.26-7.35 (m, 3H), 7.45-7.52 (m, 2H), 7.77 (s, 1H).	106.6
化合物 34		δ 3.88 (s, 3H), 5.16 (s, 2H), 6.93 (d, J = 8.4Hz, 1H), 6.99 (d, J = 7.3Hz, 1H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.26-7.35 (m, 3H), 7.44 (d, J = 7.3Hz, 1H), 7.76 (s, 1H).	108.9
化合物 35		δ 3.90 (s, 6H), 5.16 (s, 2H), 6.93 (dd, J = 2.3, 7.5Hz, 1H), 7.04-7.13 (m, 4H), 7.18 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	97.2

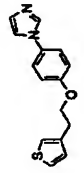
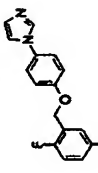
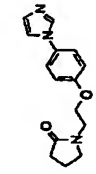
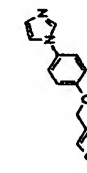
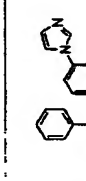
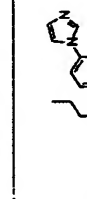
【0053】
【表6】

化合物 36		δ 2.40 (s, 3H), 5.08 (s, 2H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.23–7.33 (m, 5H), 7.41 (d, J = 7.3Hz, 1H), 7.77 (s, 1H).	100.5
化合物 37		δ 2.92–3.03 (m, 4H), 4.98 (s, 2H), 7.02 (m, J_{AB} = 8.9Hz, 2H), 7.12–7.36 (m, 10H), 7.41 (d, J = 7.8Hz, 1H), 7.77 (s, 1H).	83.5
化合物 38		δ 5.08 (s, 2H), 6.96–7.05 (m, 5H), 7.10–7.20 (m, 5H), 7.26–7.39 (m, 5H), 7.76 (s, 1H).	80.2
化合物 39		δ 2.39 (s, 3H), 5.07 (s, 2H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.15–7.32 (m, 8H), 7.76 (s, 1H).	110.6
化合物 40		δ 3.83 (s, 3H), 5.03 (s, 2H), 6.93 (m, J_{AB} = 8.7Hz, 2H), 7.04 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.37 (m, J_{AB} = 8.7Hz, 1H), 7.76 (s, 1H).	101.9
化合物 41		δ 5.16 (s, 2H), 7.08 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 8.9Hz, 2H), 7.32–7.65 (m, 9H), 7.77 (s, 1H).	87.0
化合物 42		δ 2.37 (s, 3H), 5.07 (s, 2H), 7.04 (m, J_{AB} = 8.7Hz, 2H), 7.19–7.23 (m, 4H), 7.26–7.35 (m, 4H), 7.76 (s, 1H).	97.3

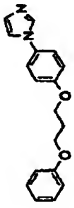
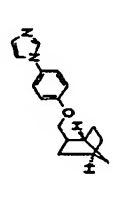
【0054】
【表7】

化合物 43		δ 3.83 (s, 3H), 4.69 (s, 2H), 7.00 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.32 (m, J_{AB} = 9.0Hz, 2H), 7.78 (s, 1H).	81.3
化合物 44		δ 5.27 (s, 2H), 7.02 (m, 1H), 7.07 (m, J_{AB} = 8.9Hz, 2H), 7.14 (d, J = 3.4Hz, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.31 (m, J_{AB} = 8.9Hz, 2H), 7.35 (m, 1H), 7.77 (s, 1H).	99.7
化合物 45		δ 2.47 (s, 3H), 3.28 (t, J = 6.4Hz, 2H), 4.18 (t, J = 6.4Hz, 2H), 6.88 (m, J_{AB} = 8.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H), 8.61 (s, 1H).	96.0
化合物 46		δ 3.34 (t, J = 6.7Hz, 2H), 4.23 (t, J = 6.7Hz, 2H), 5.95 (m, 1H), 7.00 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.19 (m, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	100.4
化合物 47		δ 1.45-1.76 (m, 6H), 3.53 (m, 1H), 3.74 (m, 1H), 3.92 (dd, J = 3.9, 10.0Hz, 1H), 4.00 (dd, J = 6.4, 10.0Hz, 1H), 4.08 (m, 1H), 7.01 (m, J_{AB} = 8.9Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H).	10.9
化合物 48		δ 4.17-4.30 (m, 3H), 4.42 (dd, J = 2.5, 11.4Hz, 1H), 4.59 (m, 1H), 6.86-6.95 (m, 4H), 7.03 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.28 (m, J_{AB} = 8.9Hz, 2H), 7.77 (s, 1H).	15.1
化合物 49		δ 2.50 (s, 3H), 5.06 (s, 2H), 7.04 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.26-7.38 (m, 6H), 7.76 (s, 1H).	95.0

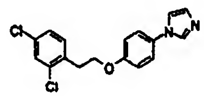
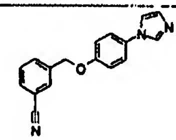
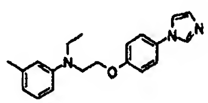
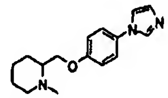
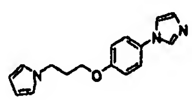
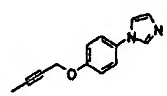
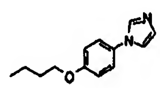
【００５５】
【表８】

化合物 50		δ 3.16 (t, J = 6.8Hz, 2H), 4.21 (t, J = 6.8Hz, 2H), 6.98 (m, J_{AB} = 8.0Hz, 2H), 7.05 (m, 1H), 7.10 (m, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.26-7.32 (m, 3H), 7.76 (s, 1H).	108.7
化合物 51		δ 5.15 (s, 2H), 6.89-7.11 (m, 4H), 7.19 (m, 3H), 7.30-7.49 (m, 2H), 7.77 (s, 1H).	102.8
化合物 52		δ 2.05 (m, 2H), 2.41 (t, J = 8.1Hz, 2H), 3.60 (t, J = 7.0Hz, 2H), 3.71 (t, J = 5.2Hz, 2H), 4.15 (t, J = 5.2Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.21 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	95.7
化合物 53		δ 5.12 (s, 2H), 7.04 (m, 8.8Hz, 2H), 7.16-7.21 (m, 3H), 7.26-7.39 (m, 4H), 7.77 (s, 1H).	108.6
化合物 54		δ 2.75 (d, J = 2.0Hz, 1H), 5.86 (d, J = 2.0Hz, 1H), 7.17-7.71 (m, 11H), 7.78 (s, 1H).	92.9
化合物 55		δ 0.94 (t, J = 7.2Hz, 6H), 1.26-1.54 (m, 4H), 1.57-1.73 (m, 4H), 4.27 (quint, J = 5.9Hz, 1H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.26 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	84.7
化合物 56		δ 2.09-2.15 (m, 2H), 2.14 (s, 3H), 2.71 (t, J = 7.0Hz, 2H), 4.11 (t, J = 6.1Hz, 2H), 6.99 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.30 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	95.0

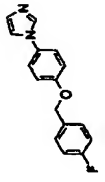
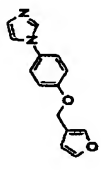
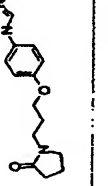
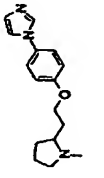
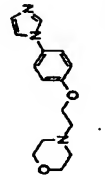
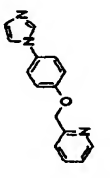
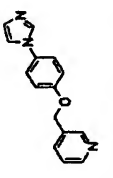
【００５６】
【表９】

化合物57		δ 2.29 (quint, J = 6.0Hz, 2H), 4.18 (t, J = 6.1Hz, 2H), 4.21 (t, J = 6.1Hz, 2H), 6.91-7.02 (m, 5H), 7.18 (s, 1H), 7.20 (s, 1H), 7.26-7.33 (m, 4H), 7.76 (s, 1H).	98.0
化合物58		δ 1.61 (s, 3H), 1.76 (s, 3H), 1.82 (s, 3H), 2.08-2.17 (m, 4H), 4.58 (d, J = 6.7Hz, 2H), 5.09 (m, 1H), 5.49 (t, J = 6.7Hz, 1H), 6.99 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.77 (s, 1H).	100.7
化合物59		δ 1.13-1.82 (m, 9H), 2.26-2.62 (m, 2H), 3.85-4.00 & 3.28-3.69 (m, 2H), 6.99 (m, J_{AB} = 9.0Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	98.1
化合物60		δ 0.87-0.94 (m, 2H), 1.08-1.33 (m, 6H), 1.43-1.53 (m, 2H), 1.63-1.83 (m, 7H), 3.98 (t, J = 6.5 Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	68.8
化合物61		δ 0.74 (s, 3H), 1.21 (s, 3H), 2.15 (dt, J = 5.1, 6.5Hz, 2H), 3.46 (d, J = 11.0Hz, 2H), 3.63 (d, J = 11.0Hz, 2H), 4.14 (t, J = 6.5Hz, 2H), 4.70 (t, J = 5.1Hz, 1H), 6.99 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	91.8
化合物62		δ 1.26 (t, J = 7.1Hz, 3H), 1.45-1.58 (m, 2H), 1.65-1.75 (m, 2H), 1.77-1.88 (m, 2H), 2.35 (t, J = 7.4Hz, 2H), 3.99 (t, J = 6.4Hz, 2H), 4.14 (q, J = 7.1Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H).	98.0
化合物63		δ 3.09 (t, J = 6.8Hz, 2H), 4.20 (t, J = 6.8Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.17-7.32 (m, 5H), 7.39 (ddd, J = 1.7, 2.1, 7.1Hz, 1H), 7.45 (d, J = 1.7Hz, 1H), 7.76 (s, 1H).	92.9

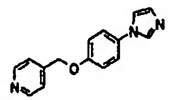
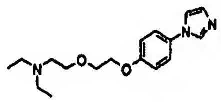
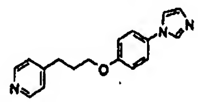
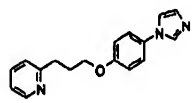
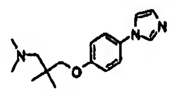
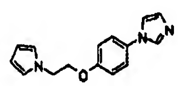
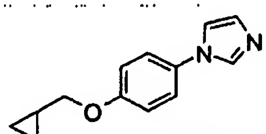
【００５７】
【表１０】

化合物 64		δ 3.23 (t, J = 6.7Hz, 2H), 4.21 (t, J = 6.7Hz, 2H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.23-7.30 (m, 4H), 7.41 (d, J = 2.2Hz, 1H), 7.76 (s, 1H).	83.2	
化合物 65		δ 5.14 (s, 2H), 7.05 (m, J_{AB} = 8.9Hz, 2H), 7.20 (s, 1H), 7.22 (s, 1H), 7.33 (m, J_{AB} = 8.9Hz, 2H), 7.50-7.56 (m, 1H), 7.64-7.70 (m, 2H), 7.77 (s, 1H).	76.9	
化合物 66		δ 1.21 (t, J = 7.2Hz, 3H), 2.32 (s, 3H), 3.48 (q J = 7.2Hz, 2H), 3.74 (t, J = 6.2Hz, 2H), 4.15 (t, J = 6.2Hz, 2H), 6.53-6.67 (m, 3H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.10-7.16 (m, 1H), 7.20 (s, 1H), 7.21 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.80 (s, 1H).	85.1	
化合物 67		δ 1.63-1.82 (m, 6H), 2.40 & 2.43 (m, 3H), 2.60-2.91 (m, 3H), 4.05 & 4.52 (m, 1H), 6.96 (m, 9.0Hz, 2H), 7.19 (d, J = 5.6Hz, 2H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	40.2	
化合物 68		δ 2.24 (tt, J = 5.9, 6.7Hz, 2H), 3.91 (t, J = 5.9Hz, 2H), 4.14 (t, J = 6.7Hz, 2H), 6.15 (dd, J = 2.0, 2.2Hz, 2H), 6.66 (dd, J = 2.0, 2.2Hz, 2H), 6.96 (m, J_{AB} = 8.9Hz, 2H), 7.20 (s, 1H), 7.21 (s, 1H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.78 (s, 1H).	110.5	
化合物 69		δ 1.88 (t, J = 2.2Hz, 3H), 4.70 (q, J = 2.2Hz, 2H), 7.06 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.22 (s, 1H), 7.32 (m, J_{AB} = 8.8Hz, 2H), 7.78 (s, 1H). mp 81.0-83.5℃	80.6	7.2
化合物 70		δ 0.99 (t, J = 7.3Hz, 3H), 1.49 (sext. J = 7.3Hz, 2H), 1.73-1.87 (m, 2H), 4.00 (t, J = 6.4Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H). mp 47.0-50.0℃	98.3	

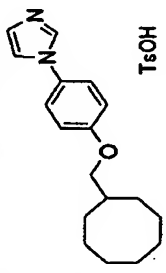
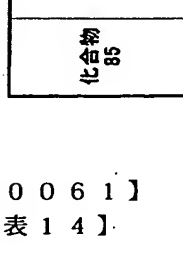
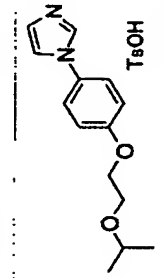
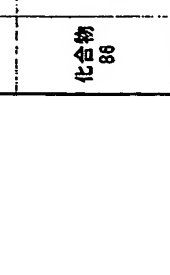
【００５８】
【表１１】

化合物 71		δ 5.07 (s, 2H), 7.03–7.46 (m, 10H), 7.77 (s, 1H). mp 91.5–93.0℃	109.0 99.3	1.3 4.7
化合物 72		δ 4.99 (s, 2H), 6.51 (d, J = 1.1Hz, 1H), 7.01–7.09 (m, 2H), 7.19–7.36 (m, 4H), 7.46 (t, J = 1.7Hz, 1H), 7.54 (dd, J = 0.9, 1.7Hz, 1H), 7.78 (t, J = 1.1Hz, 1H). mp 114.5–115.5℃		
化合物 73		δ 2.01–2.13 (m, 4H), 2.40 (t, J = 8.4Hz, 2H), 3.38–3.54 (m, 4H), 4.03 (t, J = 6.2Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H). 72.4		7.3
化合物 74		δ 2.58–2.67 (m, 4H), 2.84 (t, J = 5.7Hz, 2H), 3.71–3.78 (m, 4H), 4.15 (t, J = 5.7Hz, 2H), 6.97 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H). 55.2		33.5
化合物 75		δ 2.80 (m, 4H), 2.83 (t, J = 5.6Hz, 2H), 3.75 (m, 4H), 4.15 (t, J = 5.6Hz, 2H), 7.00 (m, J_{AB} = 8.9Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.76 (s, 1H). mp 41.0–43.5℃ 66.7		8.6
化合物 76		(200 MHz, *DMSO-d_6*) δ 5.24 (s, 2H), 7.08 (t, J = 1.1Hz, 2H), 7.10–7.21 (m, 2H), 7.37 (m, 1H), 7.50–7.63 (m, 3H), 7.65 (t, J = 1.3Hz, 1H), 7.78 (dt, J = 1.8, 7.7Hz, 1H), 8.14 (t, J = 1.1Hz, 1H), 8.60 (m, 1H). mp 94.0–95.0℃ 70.8		4.5
化合物 77		δ 5.14 (s, 2H), 7.07 (m, J_{AB} = 8.8Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.27–7.79 (m, 3H), 7.78–7.83 (m, 2H), 8.63 (dd, J = 1.8, 4.8Hz, 1H), 8.72 (d, J = 2.2Hz, 1H). mp 117.5–119.0℃ 93.7		0.83

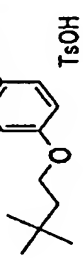
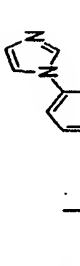
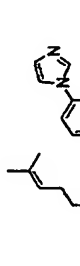
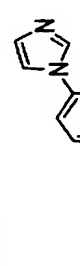
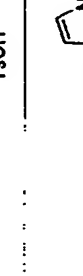
【００５９】
【表１２】

化合物 78		(200 MHz, *DMSO-d_6*) δ 5.26 (s, 2H), 7.09-7.23 (m, 3H), 7.43-7.70 (m, 5H), 8.20 (s, 1H), 8.60 (dd, J = 1.8, 4.6Hz, 2H). mp 104.0-106.0℃	95.1	4.9
化合物 79		δ 1.05 (t, J = 7.2Hz, 6H), 2.62 (q, J = 7.2Hz, 4H), 2.73 (t, J = 6.2Hz, 2H), 3.67 (t, J = 6.2Hz, 2H), 3.84 (m, 2H), 4.16 (m, 2H), 7.01 (m, J_{AB} = 9.0Hz, 2H), 7.18 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 9.0Hz, 2H), 7.76 (s, 1H).	34.8	62.6
化合物 80		δ 2.16 (ddt, J = 6.2, 7.3, 8.1Hz, 2H), 2.85 (dd, J = 7.3, 8.1Hz, 2H), 4.00 (t, J = 6.2Hz, 2H), 6.97 (m, J_{AB} = 8.9Hz, 2H), 7.15-7.22 (m, 4H), 7.30 (m, J_{AB} = 8.9Hz, 2H), 7.77 (s, 1H), 8.51-8.54 (m, 2H). mp 70.0-72.0℃	94.7	1.1
化合物 81		δ 2.28 (ddt, J = 6.2, 7.0, 8.1Hz, 2H), 3.01 (dd, J = 7.0, 8.1Hz, 2H), 4.05 (t, J = 6.2Hz, 2H), 6.97 (m, J_{AB} = 9.0Hz, 2H), 7.11-7.21 (m, 4H), 7.30 (m, J_{AB} = 9.0Hz, 2H), 7.61 (dt, J = 1.8, 7.5Hz, 1H), 7.76 (s, 1H), 8.56 (d, J = 4.0Hz, 1H). mp 64.0-66.0℃	79.0	2.1
化合物 82		δ 1.01 (s, 6H), 2.29 (s, 6H), 2.30 (s, 2H), 3.74 (s, 2H), 7.01 (m, J_{AB} = 8.8Hz, 2H), 7.19 (s, 1H), 7.20 (s, 1H), 7.29 (m, J_{AB} = 8.8Hz, 2H), 7.76 (s, 1H). mp 64.0-66.0℃	55.8	106.3
化合物 83		(200 MHz, *DMSO-d_6*) δ 4.27 (s, 4H), 6.00 (t, J = 2.2Hz, 2H), 6.85 (t, J = 2.2Hz, 2H), 7.00-7.13 (m, 3H), 7.49-7.60 (m, 2H), 7.64 (t, J = 1.3Hz, 1H), 8.13 (t, J = 1.1Hz, 1H). mp 128.5-129.0℃	110.5	0.8
化合物 84	 TsOH	*DMSO-d_6*, δ 0.36 (m, 2H), 0.60 (m, 2H), 1.25 (m, 1H), 2.29 (s, 3H), 3.91 (d, J = 7.0Hz, 2H), 7.10-7.21 (m, 4H), 7.49 (m, J_{AB} = 7.9Hz, 2H), 7.71 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.22 (dd, J = 1.5, 1.9Hz, 1H), 9.60 (dd, J = 1.3, 1.5Hz, 1H). mp 136.0-138.0℃	71.8	12.5

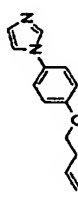
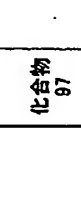
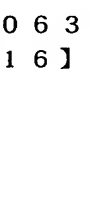
【００６０】
【表１３】

化合物 85		(200 MHz, *DMSO-d_6*), δ 1.28–2.15 (m, 15H), 2.29 (s, 3H), 3.84 (d, J = 6.8Hz, 2H), 7.08–7.25 (m, 4H), 7.48 (m, J_{AB} =8.1Hz, 2H), 7.70 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.5, 1.8Hz, 1H), 8.21 (dd, J = 1.3, 1.8Hz, 1H), 9.56 (dd, J = 1.3, 1.5Hz, 1H). mp 232.5–233.0°C	91.8	2.7
化合物 86		(200 MHz, *DMSO-d_6*) δ 1.10 (s, 3H), 1.13 (s, 3H), 2.29 (s, 3H), 3.55–3.78 (m, 3H), 4.13–4.20 (m, 2H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.2Hz, 2H), 7.48 (m, J_{AB} =8.1Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.5, 1.8Hz, 1H), 8.22 (dd, J = 1.3, 1.8Hz, 1H), 9.58 (dd, J = 1.3, 1.5Hz, 1H). mp 150.0–153.0°C	90.0	5.5
化合物 87		*DMSO-d_6*, δ 2.29 (s, 3H), 3.25 (s, 3H), 3.48 (m, 2H), 3.60 (m, 2H), 3.76 (m, 2H), 4.20 (m, 2H), 7.11 (m, J_{AB} = 8.1Hz, 2H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.23 (dd, J = 1.5, 1.9Hz, 1H), 9.61 (dd, J = 1.3, 1.5Hz, 1H). mp 113.0–1160°C	72.1	32.4
化合物 88		(200 MHz, *DMSO-d_6*) δ 1.10 (t, J = 7.0Hz, 3H), 2.29 (s, 3H), 3.38–3.65 (m, 6H), 3.74–3.83 (m, 2H), 4.15–4.25 (m, 2H), 7.12 (m, J_{AB} = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, J = 1.3, 1.8Hz, 1H), 8.22 (dd, J = 1.5, 1.8Hz, 1H), 9.59 (dd, J = 1.3, 1.5Hz, 1H). mp 117.0–117.5°C	68.4	18.5
化合物 89		(200 MHz, *DMSO-d_6*) δ 0.88 (t, J = 7.0Hz, 3H), 1.23–1.60 (m, 4H), 2.29 (s, 3H), 3.46 (t, J = 6.4Hz, 2H), 3.69–3.75 (m, 2H), 4.13–4.23 (m, 2H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, J = 1.5, 1.8Hz, 1H), 8.22 (dd, J = 1.3, 1.8Hz, 1H), 9.59 (dd, J = 1.3, 1.5Hz, 1H). mp 137.0–139.0°C	96.7	4.1
化合物 90		*DMSO-d_6*, δ 2.17 (s, 1H), 2.29 (s, 3H), 2.88 (t, J = 6.6Hz, 1H), 4.24 (t, J = 6.6Hz, 2H), 7.12 (m, J_{AB} = 8.0Hz, 2H), 7.20 (m, J_{AB} = 9.2Hz, 2H), 7.49 (m, J_{AB} = 8.0Hz, 2H), 7.73 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, J = 1.3, 1.9Hz, 1H), 8.23 (dd, J = 1.5, 1.9Hz, 1H), 9.61 (dd, J = 1.3, 1.5Hz, 1H). mp 140.0–142.0°C	91.8	7.5

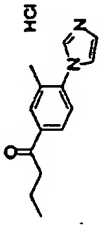
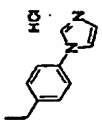
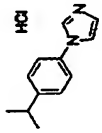
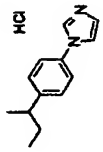
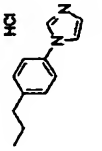
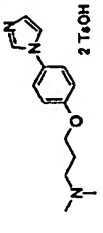
【0061】
【表14】

化合物 91		(200 MHz, *DMSO-d_6*) δ 0.98 (s, 9H), 1.68 (t, *J* = 7.0Hz, 2H), 2.29 (s, 3H), 4.11 (t, *J* = 7.0Hz, 2H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, *J* = 1.5, 1.8Hz, 1H), 8.21 (dd, *J* = 1.3, 1.8Hz, 1H), 9.58 (dd, *J* = 1.3, 1.5Hz, 1H). mp 220.0–221.0℃	101.8	1.8
化合物 92		*DMSO-d_6*, δ 0.95 (d, *J* = 6.4Hz, 6H), 1.64 (q, *J* = 6.4Hz, 2H), 1.80 (m, 1H), 2.29 (s, 3H), 4.08 (t, *J* = 6.4Hz, 2H), 7.12 (m, J_{AB} = 7.9Hz, 2H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} =7.9Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, *J* = 1.3, 1.9Hz, 1H), 8.21 (dd, *J* = 1.5, 1.9Hz, 1H), 9.59 (dd, *J* = 1.3, 1.5Hz, 1H). mp 187.0–189.0℃	102.8	2.3
化合物 93		(200 MHz, *DMSO-d_6*) δ 0.93 (d, *J* = 6.2Hz, 3H), 1.08–2.10 (m, 13H), 2.29 (s, 3H), 4.09 (t, *J* = 7.0Hz, 2H), 5.10 (m, 1H), 7.08–7.25 (m, 4H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, *J* = 1.3, 2.0Hz, 1H), 8.21 (dd, *J* = 1.5, 2.0Hz, 1H), 9.58 (dd, *J* = 1.3, 1.5Hz, 1H). mp 152.0–153.0℃	100.2	5.3
化合物 94		*DMSO-d_6*, δ 0.99 (t, *J* = 7.5Hz, 3H), 1.76 (tq, *J* = 6.6, 7.5Hz, 2H), 2.29 (s, 3H), 4.02 (t, *J* = 6.6Hz, 2H), 7.12 (m, J_{AB} = 7.9Hz, 2H), 7.17 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} =7.9Hz, 2H), 7.72 (m, J_{AB} = 9.0Hz, 2H), 7.90 (dd, *J* = 1.3, 1.9Hz, 1H), 8.22 (dd, *J* = 1.5, 1.9Hz, 1H), 9.61 (dd, *J* = 1.3, 1.5Hz, 1H). mp 148.0–150.0℃	82.7	7.7
化合物 95		(200 MHz, *DMSO-d_6*) δ 1.11 (t, *J* = 7.0Hz, 3H), 1.90–2.05 (m, 2H), 2.29 (s, 3H), 3.44 (q, *J* = 7.0Hz, 2H), 3.52 (t, *J* = 6.2Hz, 2H), 4.11 (t, *J* = 6.4Hz, 2H), 7.11 (m, J_{AB} = 8.3Hz, 2H), 7.19 (m, J_{AB} = 9.2Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, *J* = 1.5, 1.8Hz, 1H), 8.21 (dd, *J* = 1.3, 1.8Hz, 1H), 9.56 (dd, *J* = 1.3, 1.5Hz, 1H). mp 122.5–124.0℃	94.3	2.0
化合物 96		*DMSO-d_6*, δ 1.77 (t, *J* = 2.6Hz, 3H), 2.29 (s, 3H), 2.58–2.66 (m, 2H), 4.12 (t, *J* = 6.7Hz, 2H), 7.11 (d, *J*= 7.7Hz, 2H), 7.20 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.72 (m, J_{AB}= 9.0Hz, 2H), 7.89 (t, *J* = 1.5, 1.8Hz, 1H), 8.22 (t, *J* = 1.3, 1.8Hz, 1H), 9.58 (t, *J* = 1.3, 1.5Hz, 1H). mp 147.5–149.5℃	95.8	5.0

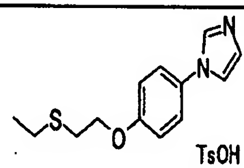
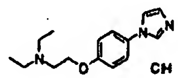
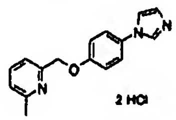
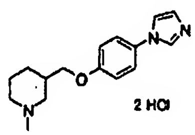
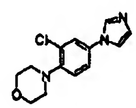
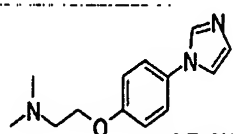
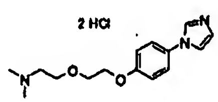
【００６２】
【表１５】

化合物 97		(200 MHz, *DMSO-d_6*) δ 2.29 (s, 3H), 2.45-2.58 (m, 2H), 4.12 (t, *J* = 6.6Hz, 2H), 5.05-5.25 (m, 2H), 5.90 (m, 1H), 7.11 (m, J_{AB} = 7.9Hz, 2H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB} = 9.0Hz, 2H), 7.80 (dd, *J* = 1.5, 1.8Hz, 1H), 8.21 (dd, *J* = 1.3, 1.8Hz, 1H), 9.58 (dd, *J* = 1.3, 1.5Hz, 1H). mp 133.5-134.5℃	101.9	2.5
化合物 98		(200 MHz, *DMSO-d_6*) δ 1.13-2.05 (m, 10H), 2.29 (s, 3H), 4.47(m, 1H), 7.11 (m, J_{AB} = 7.7Hz, 2H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.68 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, *J* = 1.5, 1.8Hz, 1H), 8.20 (dd, *J* = 1.3, 1.8Hz, 1H), 9.56 (dd, *J* = 1.3, 1.5Hz, 1H). mp 187.5-188.0℃	98.2	3.7
化合物 99		*DMSO-d_6*, δ 0.99 (d, *J* = 6.6Hz, 6H), 2.05 (m, 1H), 2.29 (s, 3H), 3.84 (d, *J* = 6.6Hz, 2H), 7.11 (d, J_{AB}= 8.1Hz, 2H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.71 (m, J_{AB}= 9.0Hz, 2H), 7.88 (t, *J* = 1.5, 1.8Hz, 1H), 8.20 (t, *J* = 1.3, 1.8Hz, 1H), 9.55 (t, *J* = 1.3, 1.5Hz, 1H). mp 176.5-178.0℃	100.6	4.3
化合物 100		(200 MHz, *DMSO-d_6*) δ 2.05-2.23 (m, 2H), 2.99 (t, *J* =7.9Hz, 2H), 4.11 (t, *J* = 6.4Hz, 2H), 7.16 (m, J_{AB} = 9.2Hz, 2H), 7.74 (m, J_{AB} = 9.2Hz, 2H), 7.88-8.03 (m, 2H), 8.23 (dd, *J* = 1.3, 1.8Hz, 1H), 8.48 (m, 1H), 8.77 (dd, *J* = 0.9 5.5Hz, 1H), 8.88 (d, *J* = 2.0Hz, 1H), 9.69 (dd, *J* = 1.3, 1.5Hz, 1H). mp 252.0-253.0℃	99.1	1.1
化合物 101		(200 MHz, *DMSO-d_6*) δ 1.28-1.85 (m, 8H), 2.69 (s, 3H), 2.72 (s, 3H), 2.91-3.10 (m, 2H), 4.07 (t, *J* = 6.4Hz, 2H), 7.18 (m, J_{AB} = 9.2Hz, 2H), 7.73 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, *J* = 1.5, 1.8Hz, 1H), 8.22 (dd, *J* = 1.3, 1.8Hz, 1H), 9.65 (dd, *J* = 1.3, 1.5Hz, 1H). mp 205.0-207.0℃	90.0	2.2
化合物 102		δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.35-1.42 (m, 2H), 1.58-1.68 (m, 2H), 2.18 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 7.21-7.28 (m, 4H), 7.62 (dd, *J* = 1.4, 1.7Hz, 1H), 8.74 (dd, *J* = 1.2, 1.4Hz, 1H). mp 152.0-153.0℃		

【００６３】
【表１６】

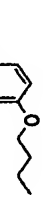
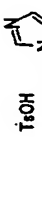
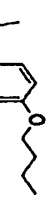
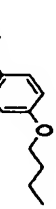
化合物103		δ 1.03 (t, J = 7.5 Hz, 3H), 1.76–1.83 (m, 2H), 2.34 (s, 3H), 2.98 (t, J = 7.3 Hz, 2H), 7.29 (dd, J = 1.3, 1.6Hz, 1H), 7.53 (d, J = 8.2Hz, 1H), 7.66 (dd, J = 1.5, 1.6Hz, 1H), 7.97 (dd, J = 1.9, 8.2Hz, 1H), 8.00 (d, J = 1.9Hz, 1H), 9.35 (dd, J = 1.3, 1.5Hz, 1H). mp 199.5–201.0℃	
化合物104		(200 MHz) δ 1.30 (t, J = 7.5 Hz, 3H), 2.76 (q, J = 7.5 Hz, 2H), 7.40–7.50 (m, 5H), 7.58 (d, J = 1.3Hz, 1H), 9.05 (s, 1H).	
化合物105		(200 MHz) δ 0.89 (t, J = 6.8 Hz, 3H), 1.13–1.43 (m, 8H), 1.50–1.75 (m, 2H), 2.70 (t, J = 7.3 Hz, 2H), 7.35–7.65 (m, 6H), 9.35 (dd, J = 1.3, 1.5Hz, 1H).	
化合物106		(200 MHz) δ 1.28 (s, 3H), 1.31 (s, 3H), 3.02 (m, 1H), 7.40–7.63 (m, 6H), 9.43 (dd, J = 1.3, 1.5Hz, 1H). mp 205.5–207.5℃	
化合物107		(200 MHz) δ 0.85 (t, J = 7.5 Hz, 3H), 1.28 (d, J = 6.8Hz, 3H), 1.55–1.75 (m, 2H), 2.83–2.84 (m, 2H), 7.38–7.53 (m, 5H), 7.59 (dd, J = 1.3, 1.8Hz, 1H), 9.13 (dd, J = 1.3, 1.5Hz, 1H). mp 142.0–146.0℃	
化合物108		(200 MHz) δ 0.97 (t, J = 7.3Hz, 3H), 1.58–1.80 (m, 2H), 2.69 (t, J = 7.3Hz, 2H), 7.35–7.55 (m, 5H), 7.59 (dd, J = 1.3, 1.8Hz, 1H), 9.29 (dd, J = 1.3, 1.5Hz, 1H). mp 155.5–157.0℃	
化合物109		*DMSO-d_6*, δ 2.29 (s, 6H), 2.29 (s, 6H), 2.83 (s, 3H), 2.85 (s, 3H), 3.24 (m, 2H), 4.13 (t, J = 6.0Hz, 2H), 7.12 (m, J_{AB} = 8.0Hz, 4H), 7.18 (m, J_{AB} = 9.0Hz, 2H), 7.49 (m, J_{AB} = 8.0Hz, 4H), 7.74 (m, J_{AB} = 9.0Hz, 2H), 7.92 (dd, J = 1.3, 1.9Hz, 1H), 8.22 (dd, J = 1.5, 1.9Hz, 1H), 9.81 (dd, J = 1.3, 1.5Hz, 1H). mp 95.0–98.0℃	35.9 50.6

【００６４】
【表１７】

化合物 110	 TsOH	*DMSO-d_6*, δ 1.21 (t, *J* = 7.5Hz, 3H), 2.29 (s, 3H), 2.64 (q, *J* = 7.5Hz, 2H), 2.91 (t, *J* = 6.6Hz, 2H), 4.23 (t, *J* = 6.6Hz, 2H), 7.11 (d, *J* = 7.9Hz, 2H), 7.20 (m, J_{AB} = 9.2Hz, 2H), 7.49 (d, *J* = 7.9Hz, 2H), 7.73 (m, J_{AB} = 9.2Hz, 2H), 7.90 (dd, *J* = 1.3, 1.9Hz, 1H), 8.22 (dd, *J* = 1.5, 1.9Hz, 1H), 9.61 (dd, *J* = 1.3, 1.5Hz, 1H). mp 147.0-149.0℃	97.9	1.8
化合物 111	 CH CH	*DMSO-d_6*, δ 1.28 (t, *J* = 7.3Hz, 6H), 3.10-3.30 (m, 4H), 3.46-3.58 (m, 2H), 4.51 (t, *J* = 5.0Hz, 2H), 7.25 (m, J_{AB} = 9.0Hz, 2H), 7.78 (m, J_{AB} = 8.9Hz, 2H), 7.90 (dd, *J* = 1.5, 1.8Hz, 1H), 8.23 (dd, *J* = 1.3, 1.8Hz, 1H), 9.66 (dd, *J* = 1.3, 1.5Hz, 1H). mp 228.0-230.0℃	33.0	49.5
化合物 112	 2 HCl	*DMSO-d_6*, δ 2.73 (s, 3H), 5.52 (s, 2H), 7.32 (m, J_{AB} = 9.2Hz, 2H), 7.68 (d, *J* = 7.9Hz, 1H), 7.73-7.83 (m, 3H), 7.92 (dd, *J* = 1.5, 1.8Hz, 1H), 8.20-8.30 (m, 2H), 9.72 (dd, *J* = 1.3, 1.5Hz, 1H). mp 236.0-237.0℃	80.4	17.6
化合物 113	 2 HCl	*DMSO-d_6*, δ 1.26 (m, 1H), 1.88 (m, 2H), 2.73 (s, 1H), 2.73-2.87 (m, 2H), 3.26-3.51 (m, 2H), 3.93 (dd, *J* = 7.3, 9.6Hz, 1H), 4.05 (dd, *J* = 4.7, 9.6Hz, 1H), 7.19 (m, J_{AB} = 9.0Hz, 2H), 7.75 (m, J_{AB} = 9.0Hz, 2H), 7.90 (d, *J* = 1.4Hz, 1H), 8.23 (d, *J* = 1.4Hz, 1H), 9.65 (d, *J* = 1.4Hz, 1H). mp 232.0-242.0℃	82.2	6.8
化合物 114		δ 3.09 (t, *J* = 4.5Hz, 4H), 3.90 (t, *J* = 4.5Hz, 4H), 7.12 (d, *J* = 8.7Hz, 1H), 7.20 (s, 1H), 7.22 (s, 1H), 7.27 (dd, *J* = 2.5, 8.7Hz, 1H), 7.45 (d, *J* = 2.5Hz, 1H), 7.79 (s, 1H). mp 127.0-129.0℃		40.8
化合物 115	 2 TsOH	*DMSO-d_6*, δ 2.29 (s, 6H), 2.89 brs, 6H), 3.57 (m, 2H), 4.41 (brt, *J* = 5.3Hz, 2H), 7.12 (brd, *J* = 7.9Hz, 4H), 7.25 (m, J_{AB} = 9.0Hz, 2H), 7.49 (brd, *J* = 7.9Hz, 4H), 7.77 (m, J_{AB} = 9.0Hz, 2H), 7.93 (t, *J* = 1.5Hz, 1H), 8.24 (t, *J* = 1.5Hz, 1H), 9.63 (d, *J* = 1.5Hz, 1H). mp 161.0-164.0℃	19.4	387.4
化合物 116	2 HCl 	*DMSO-d_6*, δ 2.76 (s, 3H), 2.77 (s, 3H), 3.27 (m, 2H), 3.80-3.91 (m, 4H), 4.25 (m, 2H), 7.21 (m, J_{AB} = 9.0Hz, 2H), 7.76 (m, J_{AB} = 9.0Hz, 2H), 7.91 (dd, *J* = 1.3, 1.9Hz, 1H), 8.24 (dd, *J* = 1.5, 1.9Hz, 1H), 9.71 (dd, *J* = 1.3, 1.5Hz, 1H). mp 174.0-179.0℃	67.2	9.0

【００６５】

【表１８】

化合物117		*DMSO-d_6*, δ 1.00 (t, J = 7.3Hz, 3H), 1.52 (m, 2H), 1.83 (m, 2H), 2.37 (s, 3H), 2.68 (s, 3H), 4.04 (t, J = 6.4Hz, 2H), 7.18-7.27 (m, 4H), 7.42 (s, 1H), 7.88 (m, J_{AB} = 8.1Hz, 2H). mp 148.0-149.0℃	>300.0
化合物118		*DMSO-d_6*, δ 0.95 (t, J = 7.3Hz, 3H), 1.45 (tq, J = 7.3, 7.7Hz, 2H), 1.67-1.80 (m, 2H), 2.17 (d, J = 0.9Hz, 3H), 2.29 (s, 3H), 4.07 (t, J = 6.5Hz, 2H), 7.09-7.21 (m, 4H), 7.48 (m, J_{AB} = 8.1Hz, 2H), 7.55 (m, J_{AB} = 8.8Hz, 2H), 9.25 (d, J = 1.5Hz, 1H). mp 163.0-164.0℃	3.4
化合物119		δ 0.99 (t, J = 7.3Hz, 3H), 1.45 (tq, J = 7.3, 7.7Hz, 2H), 1.72-1.83 (m, 2H), 2.17 (d, J = 0.9Hz, 3H), 3.99 (t, J = 6.5Hz, 2H), 6.92-7.00 (m, 1H), 6.98 (m, J_{AB} = 9.0Hz, 2H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.66 s, 1H). mp 130.0-130.5℃	173.1
化合物120		*DMSO-d_6*, δ 1.21 (t, J = 7.0Hz, 3H), 2.17 (s, 3H), 3.11-3.50 (m, 8H), 3.55 (t, J = 4.8Hz, 2H), 4.09 (q, J = 7.0Hz, 2H), 4.52 (t, J = 4.8Hz, 2H), 7.25 (m, J_{AB} = 9.0Hz, 2H), 7.58-7.64 (m, 3H), 9.26 (s, 1H). mp 212.0-214.5℃	56.5
化合物121		*DMSO-d_6*, δ 1.21 (t, J = 7.2Hz, 3H), 3.00-3.83 (m, 8H), 3.56 (t, J = 4.8Hz, 2H), 4.09 (q, J = 7.2Hz, 2H), 4.54 (t, J = 4.7Hz, 2H), 7.28 (m, J_{AB} = 9.0Hz, 2H), 7.78 (m, J_{AB} = 9.0Hz, 2H), 7.89 (dd, J = 1.4, 1.9Hz, 1H), 8.21 (dd, J = 1.4, 1.9Hz, 1H), 8.64 (t, J = 1.4Hz, 1H). mp 199.5-202.0℃	18.2

【００６６】

試験例［ヒト腎ミクロソーム由来２０－ＨＥＴＥ産生酵素の阻害作用］

上記表記載の化合物について、２０－ＨＥＴＥ産生阻害作用を試験した。

本試験はＪ．Ｐｈａｒｍａｃｏｌ．Ｅｘｐ．Ｔｈｅｒ．，第２６８巻，第４７４頁（１９９４）に記載の方法に準拠して行った。

ＤＭＳＯで１μＭに調製した被験薬溶液を、５ｍＭの塩化マグネシウム及び１ｍＭのエチ

レンジアミンテトラアセティックアシッドジソディウムソルト（ＥＤＴＡ）を含む５０ｍＭの３－モルホリノプロパンスルホン酸（ＭＯＰＳ）（ｐＨ７．４）緩衝液に加え、酵素源としてヒト腎ミクロソーム画分（Ｈｕｍａｎ Ｃｅｌｌ Ｃｕｌｔｕｒｅ Ｃｅｎｔｅｒ，Ａｎａｔｏｍｉｃ Ｇｉｆｔ Ｆｏｕｎｄａｔｉｏｎ）、基質として［５，６，８，９，１１，１２，１４，１５］トリチウムーアラキドン酸、そして補酵素としてＮＡＤＰＨを添加し、３７度で１．５時間反応させた。反応液にギ酸を添加して反応を停止させた後、アセトニトリル（終濃度５０％）を加えた。ＯＤＳカラム（バイオシルＣ１８，バイオラッド社製）を装着した放射性物質検出器付き高速液体クロマトグラフィーを用いて２０－ＨＥＴＥの産生量を測定した。

【００６７】

化合物無添加時の２０－ＨＥＴＥの産生量を１００％とし、化合物を添加した時の２０－ＨＥＴＥ産生量から、抑制率（％）を算出した。その結果を上記表１に併せて示す。

また、化合物無添加時の２０－ＨＥＴＥの産生量を１００％とし、化合物を添加した時の２０－ＨＥＴＥ産生が５０％阻害される化合物濃度（IC_{50}値）も算出した。その結果についても上記表１に併せて示す。

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(51)Int.Cl.[7]	F I	テーマコード（参考）
A61K 31/454	A61K 31/454	
A61K 31/496	A61K 31/496	
A61K 31/5377	A61K 31/5377	
A61P 9/00	A61P 9/00	
A61P 9/10	A61P 9/10	
A61P 13/12	A61P 13/12	
A61P 43/00	A61P 43/00 111	
C07D 401/12	C07D 401/12	
C07D 403/12	C07D 403/12	
C07D 405/12	C07D 405/12	
C07D 409/12	C07D 409/12	
C07D 417/12	C07D 417/12	

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